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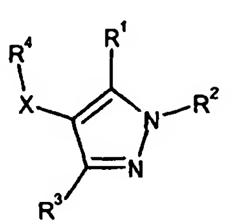
(54) Title: PYRAZOLE DERIVATIVES



(I)

(57) Abstract: This invention relates to the use of pyrazole derivatives of formula (I) and pharmaceutically acceptable salts and solvates thereof, in the manufacture of a reverse transcriptase inhibitor or modulator, to certain novel such pyrazole derivatives and to processes for the preparation of and compositions containing such novel derivatives.

PYRAZOLE DERIVATIVES

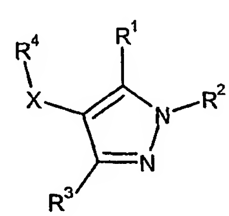
This invention relates to the use of pyrazole derivatives in the manufacture of a reverse transcriptase inhibitor or modulator, to certain novel such pyrazole derivatives and to processes for the preparation of and compositions containing such novel derivatives.

The present pyrazole derivatives bind to the enzyme reverse transcriptase and are modulators, especially inhibitors thereof. Reverse transcriptase is implicated in the infectious lifecycle of HIV, and compounds which interfere with the function of this enzyme have shown utility in the treatment of conditions including AIDS. There is a constant need to provide new and better modulators, especially inhibitors, of HIV reverse transcriptase since the virus is able to mutate, becoming resistant to their effects.

The present pyrazole derivatives are useful in the treatment of a variety of disorders including those in which reverse transcriptase is implicated. Disorders of interest include those caused by Human Immunodificiency Virus (HIV) and genetically related retroviruses, such as Acquired Immune Deficiency Syndrome (AIDS).

European Patent Application EP 0 786 455 A1 discloses a class of imidazole compounds which inhibit the growth of HIV. A class of N-phenylpyrazoles which act as reverse transcriptase inhibitors are disclosed in *J. Med. Chem.*, 2000, **43**, 1034. Antiviral activity is ascribed to a class of N-(hydroxyethyl)pyrazole derivatives in US patent number 3,303,200.

According to the present invention there is provided the use of a compound of the formula



(I)

each R^5 is independently either H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, fluoro-(C_1-C_6)-alkyl, phenyl or benzyl, or, when two such groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl and morpholinyl being optionally substituted by C_1-C_6 alkyl or C_3-C_7 cycloalkyl and said piperazinyl and homopiperazinyl being optionally substituted on the nitrogen atom not taken together with the two R^5 groups to form the ring by -COR^7 or -SO_2R^7;

R^6 is a four to six-membered, aromatic, partially unsaturated or saturated heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s), said heterocyclic group being optionally substituted by -OR^5, -NR^5R^5, -CN, oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, -COR^7 or halo;

R^7 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, fluoro-(C_1-C_6)-alkyl, phenyl or benzyl;

R^8 is C_1-C_6 alkyl substituted by phenyl, phenoxy, pyridyl or pyrimidinyl, said phenyl, phenoxy, pyridyl and pyrimidinyl being optionally substituted by halo, -CN, -$CONR^5R^5$, -$SO_2NR^5R^5$, -$NR^5SO_2R^7$, -NR^5R^5, -(C_1-C_6 alkylene)-NR^5R^5, C_1-C_6 alkyl, fluoro-(C_1-C_6)-alkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy;

R^9 is H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl, said C_1-C_6 alkyl and C_3-C_7 cycloalkyl being optionally substituted by -OR^5, -NR^5R^5, -NR^5COR^5, -$CONR^5R^5$ or R^6;

R^{10} is C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_7 cycloalkyl, phenyl, benzyl or C-linked R^6, said C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -OR^5, -OR^{12}, -CN, -CO_2R^7, -$CONR^5R^5$, -$OCONR^5R^5$, -C(=NR^5)NR^5OR^5, -$CONR^5NR^5R^5$, -$OCONR^5CO_2R^7$, -NR^5R^5, -NR^5R^{12}, -NR^5COR^5, -$NR^5CO_2R^7$, -$NR^5CONR^5R^5$, -$NR^5COCONR^5R^5$, -$NR^5SO_2R^7$, -$SO_2NR^5R^5$ or R^6;

X is -CH_2-, -CHR^{11}-, -CO-, -S-, -SO- or -SO_2-;

$-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6, said C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, $-OR^5$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5COR^5$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6,

or (ii) R^1 and R^3 are each independently C_1-C_6 alkyl, C_3-C_7 cycloalkyl or halo-(C_1-C_6 alkyl), and R^2 is H,

provided that

(a) for definition (i), R^1 and R^3 are not both H,
(b) for definition (i), R^1 and R^3 are not both optionally substituted phenyl, as defined therein,
(c) for definition (i), when R^1 and R^3 are both methyl, R^2 is not phenyl or methyl, and
(d) for definition (ii), R^1 and R^3 are not both methyl;

Y is a direct bond or C_1-C_3 alkylene;

Z is R^{10} or, where Y is C_1-C_3 alkylene, Z is $-NR^5COR^{10}$, $-NR^5CONR^5R^{10}$, $-NR^5CONR^5COR^{10}$ or $-NR^5SO_2R^{10}$;

R^4 is phenyl or pyridyl, each substituted by at least one substituent selected from halo, -CN, C_1-C_6 alkyl, fluoro-(C_1-C_6)-alkyl, C_3-C_7 cycloalkyl and C_1-C_6 alkoxy;

each R^5 is independently either H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, fluoro-(C_1-C_6)-alkyl, phenyl or benzyl, or, when two such groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl and morpholinyl being optionally substituted by C_1-C_6 alkyl or C_3-C_7 cycloalkyl and said piperazinyl and homopiperazinyl being optionally substituted on the nitrogen atom not taken together with the two R^5 groups to form the ring by $-COR^7$ or $-SO_2R^7$;

In the above definitions, halo means fluoro, chloro, bromo or iodo. Unless otherwise stated, alkyl, alkenyl, alkynyl, alkylene and alkoxy groups containing the requisite number of carbon atoms can be unbranched or branched chain. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkenyl include ethenyl, propen-1-yl, propen-2-yl, propen-3-yl, 1-buten-1-yl, 1-buten-2-yl, 1-buten-3-yl, 1-buten-4-yl, 2-buten-1-yl, 2-buten-2-yl, 2-methylpropen-1-yl or 2-methylpropen-3-yl. Examples of alkynyl include ethynyl, propyn-1-yl, propyn-3-yl, 1-butyn-1-yl, 1-butyn-3-yl, 1-butyn-4-yl, 2-butyn-1-yl. Examples of alkylene include methylene, 1,1-ethylene, 1,2-ethylene, 1,1-propylene, 1,2-propylene, 2,2-propylene and 1,3-propylene. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. 'C-linked' used in the definition of R^{10} means that the R^{10} substituent is attached through a ring carbon atom. Where R^1 and R^2 are taken together, they form, along with the nitrogen atom and the carbon atom of the pyrazole ring to which they are attached, a 5- or 6-membered ring.

The pharmaceutically acceptable salts of the compounds of the formula (I) and the compounds of the formula (Ib) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, para-toluenesulphonate and pamoate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

For a review on suitable salts see Berge *et al*, *J. Pharm. Sci.*, **66**, 1-19, 1977.

2-[4-[(3,5-dichlorophenyl)sulfanyl]-3-ethyl-5-(hydroxymethyl)-1*H*-pyrazol-1-yl]ethanol; and
2-{4-[(3,5-dichlorophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol.

The following preferred features of the invention relate both to compounds of the formula (I) and compounds of the formula (Ib).

Preferably, R^1 is C_1-C_6 alkyl, $-OR^7$, $-CO_2R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5CO-(C_1$-C_6 alkylene)$-OR^5$ or R^6, said C_1-C_6 alkyl being optionally substituted by halo, -CN, $-OR^5$, $-OR^8$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^8R^9$, $-NR^5COR^5$, $-NR^5COR^6$, $-NR^5COR^8$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6.
Preferably, R^1 is C_1-C_6 alkyl, $-OR^7$, $-CO_2R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5CO-(C_1$-C_6 alkylene)$-OR^5$ or R^6, said C_1-C_6 alkyl being optionally substituted by halo or $-OR^5$.
Preferably, R^1 is C_1-C_3 alkyl, $-OCH_3$, $-CO_2(C_1$-C_2 alkyl), $-NHCO_2(C_1$-C_2 alkyl), $-NH_2$, $-N(CH_3)_2$, $-NHCOCH_2OCH_3$ or furanyl, said C_1-C_3 alkyl being optionally substituted by fluoro or -OH.
Preferably, R^1 is methyl, ethyl, prop-2-yl, hydroxymethyl, trifluoromethyl, $-OCH_3$, $-CO_2CH_2CH_3$, $-NHCO_2CH_2CH_3$, $-NH_2$, $-N(CH_3)_2$, $-NHCOCH_2OCH_3$ or furan-2-yl.
Preferably, R^1 is ethyl.
Preferably, R^1 is methyl, ethyl, trifluoromethyl or $-CH_2NHCH_2$(4-cyanophenyl).

Preferably, R^2 is H, C_1-C_6 alkyl, $-(C_1$-C_3 alkylene)$-NR^5CO-(C_1$-C_6 alkyl), $-(C_1$-C_3 alkylene)$-NR^5CONR^5-(C_1$-C_6 alkyl), $-(C_1$-C_3 alkylene)$-NR^5CONR^5CO$-(phenyl), $-(C_1$-C_3 alkylene)$-NR^5SO_2$(C-linked R^6), $-(C_1$-C_3 alkylene)$-NR^5CO$(C-linked R^6), $-(C_1$-C_3 alkylene)$-NR^5CO$-(phenyl), each C_1-C_6 alkyl and phenyl being optionally substituted by halo, $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-OCONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-OCONR^5CO_2R^7$, $-NR^5R^5$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5CO_2R^7$, $-NR^5CONR^5R^5$, $-NR^5COCONR^5R^5$, $-NR^5SO_2R^7$, $-SO_2NR^5R^5$ or R^6.
Preferably, R^2 is H, C_1-C_6 alkyl, $-(C_1$-C_3 alkylene)$-NR^5CO-(C_1$-C_6 alkyl), $-(C_1$-C_3 alkylene)$-NR^5CONR^5-(C_1$-C_6 alkyl), $-(C_1$-C_3 alkylene)$-NR^5CONR^5CO$-(phenyl), $-(C_1$-C_3 alkylene)$-NR^5SO_2R^6$, $-(C_1$-C_3 alkylene)$-NR^5COR^6$, $-(C_1$-C_3 alkylene)$-NR^5CO$-(phenyl), each C_1-C_6 alkyl and phenyl being optionally substituted by halo, $-OR^5$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-OCONR^5R^5$, $-OCONR^5CO_2R^7$, $-NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5COCONR^5R^5$ or R^6.

-OH.

Preferably, R^3 is methyl, ethyl, prop-2-yl, hydroxymethyl, cyanomethyl, trifluoromethyl, $-CO_2CH_2CH_3$, $-CONH_2$, $-NHCO_2C(CH_3)_3$, $-N(CH_3)_2$ or $-NH_2$.

Preferably, R^3 is methyl, ethyl, prop-2-yl or trifluoromethyl.

Preferably, R^3 is ethyl.

Preferably, X is $-CH_2-$, $-CHR^{11}-$, -CO-, -S- or $-SO_2-$.

Preferably, X is $-CH_2-$, $-CH(OCH_3)-$, -CO-, -S- or $-SO_2-$.

Preferably, X is $-CH_2-$ or -S-.

Preferably, R^6 is azetidinyl, tetrahydropyrrolyl, piperidinyl, azepinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepinyl, morphoninyl, piperazinyl, diazepinyl, pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyranyl, pyridazinyl, pyrimidinyl or pyrazinyl each being optionally substituted by $-OR^5$, $-NR^5R^5$, -CN, oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, $-COR^7$ or halo.

Preferably, R^6 is furan-2-yl, 2,4-dihydroxypyrimidinyl, 1-methylimidazolyl, tetrahydrofuranyl, 1,5-dimethylpyrazolyl, tetrazolyl, pyridinyl, pyrimidinyl, 3-hydroxypyridazinyl, 2-hydroxypyridinyl, 2-oxo-2H-pyranyl or 1,2,3-thiadiazolyl.

Preferably, R^6 is 2,4-dihydroxypyrimidinyl, 1-methylimidazolyl, tetrahydrofuranyl, 1,5-dimethylpyrazolyl, tetrazolyl, pyridinyl, pyrimidinyl, 3-hydroxypyridazinyl, 2-hydroxypyridinyl, 2-oxo-2H-pyranyl or 1,2,3-thiadiazolyl.

Preferably, R^{10} is C_1-C_6 alkyl, phenyl, or C-linked R^6, said C_1-C_6 alkyl and phenyl being optionally substituted by halo, $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-OCONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-OCONR^5CO_2R^7$, $-NR^5R^5$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5CO_2R^7$, $-NR^5CONR^5R^5$, $-NR^5COCONR^5R^5$, $-NR^5SO_2R^7$, $-SO_2NR^5R^5$ or R^6.

Preferably, R^{10} is C_1-C_6 alkyl, phenyl, or C-linked R^6, said C_1-C_6 alkyl and phenyl being optionally substituted by halo, $-OR^5$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-OCONR^5R^5$, $-OCONR^5CO_2R^7$, $-NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5COCONR^5R^5$ or R^6.

Preferably, R^{10} is C_1-C_3 alkyl, phenyl, or R^6, said C_1-C_3 alkyl and phenyl being optionally substituted by fluoro, -OH, $-O(C_1$-C_6 alkyl), -CN, $-CO_2(C_1$-C_6 alkyl), $-CONH_2$, $-OCONH_2$, $-OCONHCO_2Ph$, $-NH_2$, $-N(C_1$-C_6 alkyl$)_2$, $-NHCONH_2$,

Preferably, R^4 is phenyl substituted by at least one substituent selected from halo, -CN and C_1-C_3 alkyl.

Preferably, R^4 is phenyl substituted by at least one substituent selected from fluoro, chloro, bromo, -CN and methyl.

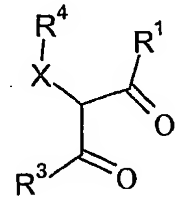
Preferably, R^4 is 3-chlorophenyl, 4-chlorophenyl, 3-fluorophenyl, 3,5-dichlorophenyl, 2,6-difluorophenyl, 3,5-difluorophenyl, 3,5-dicyanophenyl, 3,5-dibromophenyl or 3,5-dimethylphenyl.

Preferably, R^4 is (i) phenyl substituted at the 3 position by fluoro, chloro, methyl or cyano or (ii) phenyl substituted at the 3 and 5 positions by two substituents independently chosen from fluoro, chloro, methyl and cyano.

All of the compounds of the formula (I) and the compounds of the formula (Ib) can be prepared by conventional routes such as by the procedures described in the general methods presented below or by the specific methods described in the Examples section, or by similar methods thereto. The present invention also encompasses any one or more of these processes for preparing the compounds of formula (Ib).

In the following general methods, R^1, R^2, R^3, R^4 and X are as previously defined for a compound of the formula (Ib) or a compound of the formula (I) unless otherwise stated.

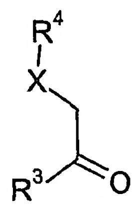
Compounds of the formula (Ib) and compounds of the formula (I) in which R^1 and R^3 are each either H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, $-CO_2R^5$, $-CONR^5R^5$, or C-linked R^6, optionally substituted where allowed, may be prepared by the reaction of a compound of the formula

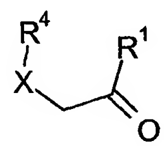

(II)

with a compound of the formula

the formula (Ib) or compounds of the formula (I) in which R^1 or R^3, respectively, is H.

Compounds of the formula (IV) in which R^1 *is H and* L^1 *is dimethylamino may be* prepared by the reaction of a compound of the formula (VI) with dimethylformamide dimethylacetal at an elevated temperature, preferably at about 100°C. Compounds of the formula (V) in which R^3 is H and L^2 is dimethylamino may be prepared by the reaction of a compound of the formula (VII) under the same conditions. Other compounds of the formula (IV) or (V) in which L^1 or L^2 is dimethylamino may be prepared analogously.


(VI)


(VII)

Compounds of the formula (VI) are either commercially available or may be prepared by methods well know in the art. For example, where X is S, compounds of the formula (VI) may be prepared by the reaction of a compound of the formula

$$R^3COCH_2Br \text{ (VIII)}$$

with a compound of the formula

$$R^4SH \text{ (IX).}$$

In a typical procedure a solution of a compound of the formula (VIII) in a suitable solvent, such as acetone, is treated with a compound of the formula (IX), optionally treated with a base, such as potassium carbonate and optionally treated with a catalyst such as sodium iodide or tetrabutylammonium iodide. The reaction is preferably performed at room temperature.

of the compound of the formula (XI) in a suitable solvent, such as ethanol or a mixture of ethanol and ethyl acetate, under a hydrogen atmosphere, is treated with 5% w/w palladium on barium sulphate. In another typical procedure, a solution of the compound of the formula (XI) in a suitable solvent, such as dichloromethane, is treated with diphenylsilane, tetrakis(triphenylphosphine)palladium (0) and zinc chloride. In a further typical example, a solution of the compound of the formula (XI) in a suitable solvent, such as dichloromethane, is treated with triethylsilane and trifluoroacetic acid.

Compounds of the formula (XI) may be prepared by the condensation of a compound of the formula (XII) with a compound of the formula

$$R^4CHO \text{ (XV)},$$

or a functional equivalent thereof, such as an acetal, optionally in the presence of a suitable catalyst, such as a mixture of acetic acid and piperidine. In a typical procedure, a solution of the compound of the formula (XII) in a suitable solvent such as toluene is treated with a compound of the formula (XV), acetic acid and piperidine and heated at a temperature of from room temperature to the reflux temperature of the solvent. Preferably, the reaction mixture is heated under reflux using a Dean-Stark apparatus. Compounds of the formula (XI), prepared in this way, in which R^1 and R^3 are different, are usually formed as a mixture of stereoisomers. Such a mixture may be used directly in subsequent transformations or separated into its individual stereoisomers which may then be used separately.

Alternatively, compounds of the formula (II) in which X is $-CH_2-$ may be prepared by the reaction of a compound of the formula (XII) with a compound of the formula

$$R^4CH_2L^6 \text{ (XXVIII)}$$

in which L^6 is a suitable leaving group, preferably is chloro, bromo, iodo or para-toluenesulphonate, in the presence of a suitable base. In a typical procedure, a

piperidine and heated at a temperature of from room temperature to the reflux temperature of the solvent. Preferably, the reaction mixture is heated under reflux using a Dean-Stark apparatus. Compounds of the formula (XIII), prepared in this way, in which R^1 and R^3 are different, are usually formed as a mixture of stereoisomers. Such a mixture may be used directly in subsequent transformations or separated into its individual stereoisomers which may then be used separately.

Compounds of the formula (II) in which X is -S- may be prepared by the reaction of a compound of the formula (XIV) with a compound of the formula (IX). In a typical procedure a solution of a compound of the formula (XIV) in a suitable solvent, such as acetone, is treated with a compound of the formula (IX), optionally treated with a base, such as potassium carbonate and optionally treated with a catalyst such as sodium iodide or tetrabutylammonium iodide. The reaction is preferably performed at room temperature.

Compounds of the formula (XIV) may be prepared by the reaction of a compound of the formula (XII) with a suitable activating agent, e.g. in the case where L^3 is chloro, with a chlorinating agent such as sulphuryl chloride. In a typical procedure, where L^3 is chloro, the compound of the formula (XII) is treated with sulphuryl chloride, optionally in the presence of a suitable solvent such as dichloromethane.

Compounds of the formula (Ib) and compounds of the formula (I) in which R^1 or R^3 is $-OR^7$ may be prepared using the route shown in Scheme 2 in which R^a is C_1-C_6 alkyl and L^4 is a suitable leaving group, preferably trifluoromethanesulphonate.

R^7OH (XXV)

in the presence of a suitable catalyst, preferably a palladium catalyst, and carbon monoxide. In a typical procedure a mixture of the compound of the formula (XVII), a suitable palladium catalyst such as 1,1'-bis(diphenylphosphino)ferrocenepalladium(II)chloride, the alcohol of the formula (XXV) and, optionally, a suitable solvent such as N,N-dimethylformamide is heated, preferably to about 50°C, under an atmosphere of carbon monoxide, preferably at a pressure of 345 kPa.

Compounds of the formula (XVII) may be prepared by the derivatisation of a compound of the formula (XVIII). In the case where L^4 is trifluoromethanesulphonate a suitable derivatising agent is phenyltriflamide. In a typical procedure, where L^4 is trifluoromethanesulphonate, a solution of the compound of the formula (XVIII) and a suitable base, preferably a trialkylamine base such as triethylamine, in a suitable solvent such as dichloromethane is treated with phenyltriflamide.

Compounds of the formula (XVIII) may be prepared by the reaction of a compound of the formula (XIX) with a compound of the formula (III), or a salt or hydrate thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (XIX) in a suitable solvent, such as ethanol, is treated with the compound of the formula (III), or the salt or hydrate thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux.

Compounds of the formula (XIX) may be prepared by the derivatisation of a compound of the formula (XX) in the same way that compounds of the formula (II) may be prepared by the derivatisation of a compound of the formula (XII) as described above.

Compounds of the formula (XX) are either commercially available or are readily prepared by methods well known to the skilled person.

In Scheme 2, compounds of the formula (Ib) and compounds of the formula (I) in which R^3 is $-OR^7$ may be prepared from a compound of the formula (XXIV) in the same way that a compound of the formula (I) or a compound of the formula (Ib) in which R^1 is $-OR^7$ is prepared from a compound of the formula (XX), as described above, *mutatis mutandis*.

The skilled man will appreciate that compounds of the formula (XVIII) and compounds of the formula (XXII) may exist in one of several tautomeric forms.

Alternatively, compounds of the formula (Ib) and compounds of the formula (I) in which R^1 or R^3 is $-OR^7$ may be prepared from compounds of the formula (XVIII) or (XXII), respectively, by reaction with a compound of the formula (XXV) under dehydrating conditions, e.g. using the Mitsunobu reaction. In a typical procedure, a solution of the compound of the formula (XVIII) or (XXII) in a suitable solvent, such as tetrahydrofuran is treated with a dialkylazodicarboxylate, preferably diethylazodicarboxylate, a triarylphosphine, preferably triphenylphosphine and a compound of the formula (XXV).

Alternatively, compounds of the formula (Ib) and compounds of the formula (I) in which R^1 or R^3 is $-OR^7$ may be prepared from compounds of the formula (XVIII) or (XXII), respectively, by reaction with a compound of the formula

$$R^7L^7 \quad (XXIX)$$

in which L^7 is a suitable leaving group, preferably halo, optionally in the presence of a suitable base. In a typical procedure, a solution of the compound of the formula (XVIII) or the compound of the formula (XXII) in a suitable solvent, such as tetrahydrofuran, dimethylformamide or ethanol, is treated with a base, such as sodium ethoxide or sodium carbonate, and the compound of the formula (XXIX), optionally with heating.

Compounds of the formula (Ib) and compounds of the formula (I) in which R^1 or R^3 is halo may be prepared by the reaction, respectively, of a compound of the formula (XVIII) or a compound of the formula (XXII) with a suitable halogenating agent. In a typical procedure, the compound of the formula (XVIII) or (XXII) is treated with $POCl_3$, optionally in the presence of a suitable solvent such as dimethylformamide, to give a compound of the formula (Ib) or a compound of the formula (I) in which R^1 or R^3, respectively, is chloro.

Compounds of the formula (Ib) and compounds of the formula (I) in which R^1 or R^3 is $-OCONR^5R^5$ may be prepared by the reaction, respectively, of a compound of the formula (XVIII) or a compound of the formula (XXII) with a compound of the formula

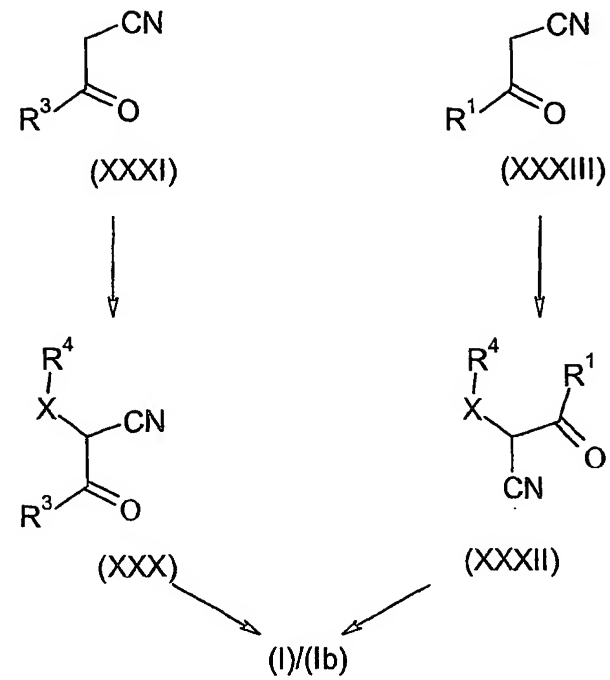
$$R^5R^5NCOL^5 \text{ (XXVI)}$$

in which L^5 is a suitable leaving group, preferably chloro, or, in the case where one of the R^5 groups is H, with a compound of the formula

$$R^5N{=}C{=}O \text{ (XXVII).}$$

Compounds of the formula (Ib) and compounds of the formula (I) in which R^1 or R^3 is $-NH_2$ may be prepared by the route shown in Scheme 3.

Scheme 3



In Scheme 3, compounds of the formula (Ib) and compounds of the formula (I) in which R^1 is $-NH_2$ may be prepared by the reaction of a compound of the formula (XXX) with a compound of the formula (III), or a salt or hydrate thereof, optionally in the presence of an acid or a base, the base preferably being a tertiary amine base such as triethylamine and the acid preferably being acetic acid. In a typical procedure, a solution of the compound of the formula (XXX) in a suitable solvent, such as ethanol, is treated with the compound of the formula (III), or the salt or hydrate thereof, and, if used, the appropriate acid or base, at a temperature of from room temperature to the reflux temperature of the solvent. In a preferred procedure, the reaction mixture is heated under reflux.

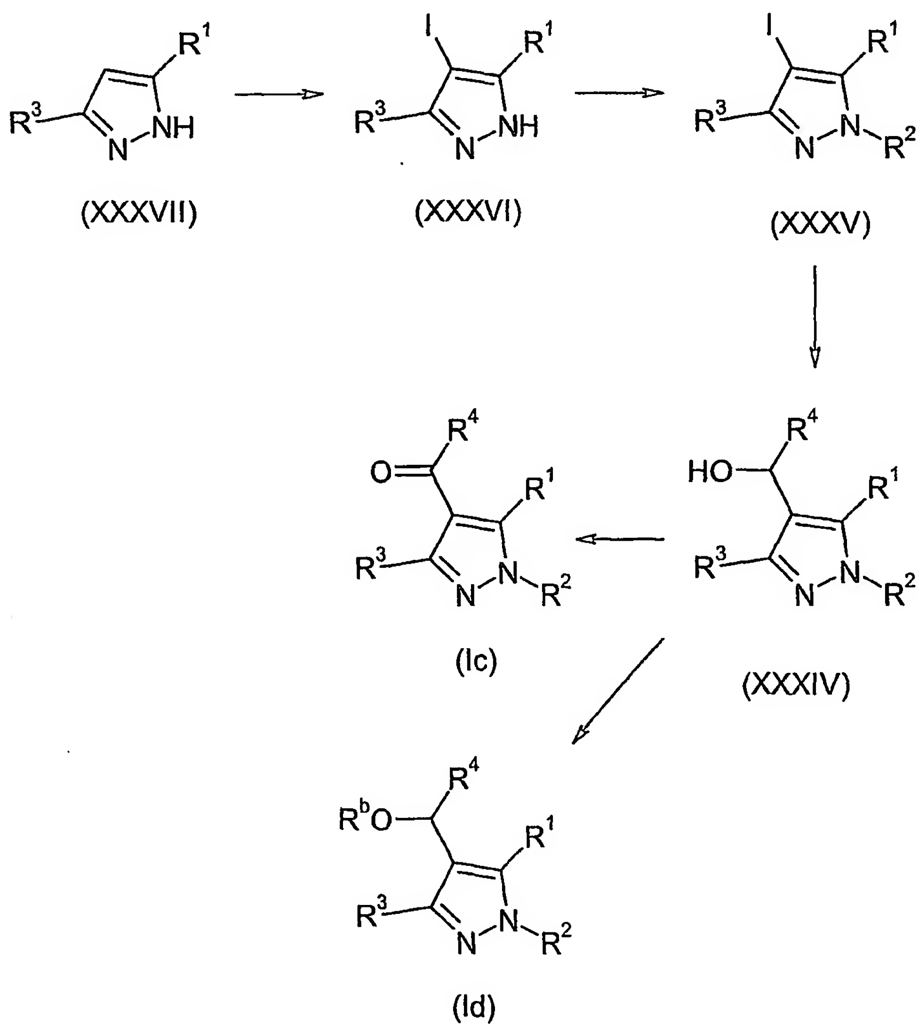
Compounds of the formula (XXX) may be prepared from a compound of the formula (XXXI) in the same way that compounds of the formula (II) may be prepared from a compound of the formula (XII) as described above.

Compounds of the formula (XXXI) are either commercially available or readily prepared by methods well known to the skilled person.

In Scheme 3, compounds of the formula (Ib) and compounds of the formula (I) in which R^3 is $-NH_2$ may be prepared from a compound of the formula (XXXIII) in the same way that compounds of the formula (Ib) and compounds of the formula (I) in which R^1 is NH_2 may be prepared from compounds of the formula (XXXI), *mutatis mutandis*.

Compounds of the formula (Ib) and compounds of the formula (I) in which X is -CO- or $-CHR^{10}-$ and R^{10} is C_1-C_6 alkoxy may be prepared by the route shown in Scheme 4 in which R^b is C_1-C_6 alkyl.

<u>Scheme 4</u>



In Scheme 4, compounds of the formula (Ib) and compounds of the formula (I) in which X is -CO- (i.e. compounds of the formula (Ic)) may be prepared by the oxidation of a compound of the formula (XXXIV). In a typical procedure, a solution of a compound of the formula (XXXIV) in a suitable solvent, such as dichloromethane, is treated with N-methylmorpholine-N-oxide and tetra-n-propylammonium perruthenate[(VII)].

Compounds of the formula (Ib) and compounds of the formula (I) in which X is -CHR^{10}- and R^{10} is C_1-C_6 alkoxy (i.e. compounds of the formula (Id)) may be prepared by the alkylation of a compound of the formula (XXXIV). In a typical procedure, a solution of a compound of the formula (XXXIV) in a suitable solvent, such as N,N-dimethylformamide, is treated with a base, such as sodium hydride, and a compound of the formula

$$R^bL^8 \text{ (XXXVIII)}$$

wherein R^b is C_1-C_6 alkyl and L^8 is a suitable leaving group, preferably chloro, bromo or iodo.

Compounds of the formula (XXXIV) may be prepared by the reaction of a compound of the formula (XXXV) with a suitable metal or organometallic reagent to form an organometallic intermediate which is reacted with a compound of the formula (XV). A preferred metal is magnesium. In a typical procedure, a solution of the compound of the formula (XXXV) in a suitable solvent, such as tetrahydrofuran, is treated with an alkylmagnesium chloride, e.g. iso-propylmagnesium chloride, preferably with cooling in an ice bath, and a compound of the formula (XV) is added.

Compounds of the formula (XXXV) may be prepared by the reaction of a compound of the formula (XXXVI) with a suitable base, preferably sodium hydride, and the addition of a compound of the formula

$$R^2L^9 \text{ (XXXIX)}$$

wherein L^9 is a suitable leaving group, preferably a chloro, bromo, iodo or tosylate group. In a typical procedure, a solution of the compound of the formula (XXXVI) in a suitable solvent, such as N,N-dimethylformamide, is treated firstly with a suitable base, such as sodium hydride, and then with a compound of the formula (XXXIX). The reaction is then preferably heated, most preferably to 50°C. If R^2 contains a free -OH, -NH_2, or -NH- group then a protecting group is preferably employed to mask such functionality. Examples of suitable protecting groups will be apparent to the skilled person [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)' by Theodora W. Green and Peter G. M. Wuts, 1991, John Wiley and Sons]. The protecting group may be removed immediately or carried through subsequent steps, as described above, and removed as a final step (see below).

Compounds of the formula (XXXVI) may be prepared by the reaction of a compound of the formula (XXXVII) with a suitable iodinating agent. In a typical procedure, a solution of the compound of the formula (XXXVII) in a suitable solvent, such as dichloromethane, is treated with the iodinating agent which is preferably N-iodosuccinimide.

Compounds of the formula (XXXVII) are either commercially available or are readily prepared by methods well known to the skilled man. Such compounds may, for instance, be prepared by analogy with the methods presented above, for example by the reaction of a diketone (XII) with a compound of the formula (III), or a salt or solvate thereof.

It will be appreciated by those skilled in the art that, in many cases, compounds of the formula (Ib) and compounds of the formula (I) may be converted, respectively, into other compounds of the formula (Ib) or compounds of the formula (I) by functional group transformations. For instance:

(a) Compounds of the formula (Ib)/(I) in which R^2 is H may be converted into compounds of the formula (Ib)/(I) in which R^2 is optionally substituted C_1-C_6 alkyl by reaction with an appropriate alkylating agent. In a typical procedure, a solution

of a compound of the formula (Ib)/(I) in which R^2 is H in a suitable solvent such as ethanol or N,N-dimethylformamide is treated with an alkyl bromide and a base such as sodium ethoxide or sodium hydride and heated at a temperature of from room temperature to the reflux temperature of the solvent. A preferred combination is N,N-dimethylformamide as the solvent, sodium hydride as the base and room temperature as the temperature. Examples of specific alkylating agents include bromoacetonitrile, ethyl 4-chloroacetoacetate, ethyl bromoacetate, methyl bromoacetate and chloroethylamine hydrochloride. The use of further specific alkylating agents is illustrated by the Examples below.

(b) Compounds of the formula (Ib)/(I) in which R^2 contains as ester functionality may be reduced with a suitable reducing agent, such as lithium aluminium hydride, to give corresponding compounds of the formula (Ib)/(I) in which R^2 contains a hydroxy group. In a typical procedure, a solution of the compound of the formula (Ib)/(I), in which R^2 contains an ester group, in a suitable solvent, such as diethyl ether, is treated with lithium aluminium hydride, preferably with cooling to a temperature of from -78 °C to 0 °C.

(c) Compounds of the formula (Ib)/(I) in which R^1 or R^3 is $-NH_2$, may be converted into compounds of the formula (Ib)/(I) in which R^1 or R^3, respectively, is $-NHR^c$, where R^c is C_1-C_6 alkyl, C_3-C_8 cycloalkyl or benzyl by a reductive amination with an appropriate aldehyde or ketone. In a typical reductive amination, the reaction will proceed in a suitable solvent such as dichloromethane, in the presence of a suitable reducing agent such as sodium triacetoxyborohydride and optionally in the presence of an acid such as acetic acid. A further reductive amination may be performed on a compound of the formula (Ib)/(I) in which R^1 or R^3 is $-NHR^c$ to give a compound of the formula (Ib)/(I) in which R^1 or R^3, respectively, is $-NR^cR^c$, where R^c is as defined above and each R^c may be the same or different.

(d) Compounds of the formula (Ib)/(I) in which R^1 or R^3 is $-NHR^5$, may be converted into compounds of the formula (Ib)/(I) in which, respectively, R^1 is $-NR^5COR^5$, $-NR^5CONR^5R^5$, $-NR^5CO_2R^7$ or $-NR^5SO_2R^7$ or R^3 is $-NR^5COR^5$,

$-NR^5CONR^5R^5$, $-NR^5CO_2R^7$ or $-NR^5SO_2R^7$ by reaction with an appropriate acylating or sulphonylating agent in a suitable inert solvent, such as dichloromethane, optionally in the presence of a base, preferably a tertiary amine base such as triethylamine.

(e) compounds of the formula (Ib)/(I) in which R^1 or R^3 is $-CO_2R^5$, wherein R^5 is other than H, may be converted into compounds of the formula (Ib)/(I) in which R^1 or R^3, respectively, is $-CO_2H$ by hydrolysis. Typically the reaction will be carried out in a suitable solvent, such as aqueous ethanol, or aqueous 1,4-dioxan and in the presence of a base such as sodium hydroxide. Such an acid may be converted to a primary amide by reaction with ammonia and a suitable coupling agent, such as a carbodiimide, e.g. dicyclohexylcarbodiimide. Such a primary amide may then be converted into a nitrile by dehydration with a suitable dehydrating agent, such as phosphoryl chloride.

(f) Compounds of the formula (Ib)/(I) in which R^1 or R^3 is $-CO_2H$, may be converted into compounds of the formula (Ib)(I) in which R^1 or R^3, respectively, is $-NH_2$, by the Curtius rearrangement. In a typical procedure, the reaction is carried out in a suitable solvent, such as dichloromethane, in the presence of a reagent such as diphenylphosphoryl azide.

(g) Compounds of the formula (Ib)/(I) in which X is -S- may be converted into compounds of the formula (Ib)/(I) in which X is -SO- by reaction with a suitable oxidising agent, such as meta-chloroperoxybenzoic acid. The reaction is carried out in the presence of a suitable solvent such as dichloromethane.

(h) Compounds of the formula (Ib)/(I) in which X is -S- may be converted into compounds of the formula (Ib)/(I) in which X is $-SO_2-$ by reaction with a suitable oxidising agent such as Oxone (trade mark), meta-chloroperoxybenzoic acid or hydrogen peroxide. In a typical procedure, a solution of the compound of the formula (Ib)/(I) in which X is -S- in a suitable solvent, such as dichloromethane, is treated with meta-chloroperoxybenzoic acid.

(i) Compounds of the formula (Ib)/(I) in which R^1, R^2 or R^3 contain a heterocycle of the formula R^6 may be prepared by standard heterocycle-forming reactions well known to the skilled person (see, for example, Advanced Organic Chemistry, 3rd Edition, by Gerry March or Comprehensive Heterocyclic Chemistry, A.R. Katritzky, C.W. Rees, E.F.V. Scriven, Volumes 1-11), either from another compound of the formula (Ib)/(I) or otherwise. For instance, compounds of the formula (Ib)/(I) in which R^2 is (2-amino-6-hydroxypyrimidin-4-yl)methyl may be prepared by the sequential reaction of a compound of the formula (Ib)/(I) in which R^2 is H with methyl 4-chloroacetoacetate and then guanidine hydrochloride.

(j) Compounds of the formula (Ib)/(I) in which either R^1 or R^3 is an N-linked heterocycle of the formula R^6 may be prepared from compounds of the formula (Ib)/(I) in which R^1 or R^3, respectively, is $-NH_2$, by standard heterocycle-forming reactions well known to the skilled man (see, for example, Advanced Organic Chemistry, 3rd Edition, by Gerry March or Comprehensive Heterocyclic Chemistry, A.R. Katritzky, C.W. Rees, E.F.V. Scriven, Volumes 1-11).

Compounds of the formula (Ib)/(I) containing an -OH, -NH- or $-NH_2$ group may be prepared by the deprotection of the corresponding compound bearing an $-OP^1$, $-NP^1-$ or $-NHP^1$ group, respectively, wherein the group P^1 is a suitable protecting group. Examples of suitable protecting groups will be apparent to the skilled person [see, for instance, 'Protecting groups in Organic Synthesis (Second Edition)' by Theodora W. Green and Peter G. M. Wuts, 1991, John Wiley and Sons]. Such compounds bearing an $-OP^1$, $-NP^1-$ or $-NHP^1$ group may be prepared using the routes described above, *mutatis mutandis*.

The compounds of the formula (I) and the compounds of the formula (Ib) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the formula (I) and the compounds of the formula (Ib) can be administered orally, buccally or sublingually in the form of

tablets, capsules, multi-particulates, gels, films, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The compounds of the formula (I) and the compounds of the formula (Ib) may also be administered as fast-dispersing or fast-dissolving dosage forms or in the form of a high energy dispersion or as coated particles. Suitable formulations of the compounds of the formula (I) and the compounds of the formula (Ib) may be in coated or uncoated form, as desired.

Such solid pharmaceutical compositions, for example, tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

General Example

A formulation of the tablet could typically contain between about 0.01mg and 500mg of active compound whilst tablet fill weights may range from 50mg to 1000mg. An example of a formulation for a 10mg tablet is illustrated below:

Ingredient	%w/w
Compound of the formula (I)/(Ib) or salt	10.000*
Lactose	64.125
Starch	21.375
Croscarmellose sodium	3.000
Magnesium Stearate	1.500

* Quantity adjusted in accordance with drug activity.

The tablets are manufactured by a standard process, for example, direct compression or a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the formula (I) and the compounds of the formula (Ib) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of the formula (I) and the compounds of the formula (Ib) can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion or needleless injection techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) and the compounds of the formula (Ib) will usually be from 0.01 to 30 mg/kg, preferably from 0.01 to 10 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the formula (I) or the compound of the formula (Ib) may contain from 1 to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any

individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will appreciate that, in the treatment of certain conditions the compounds of the formula (I) and the compounds of the formula (Ib) may be taken as a single dose as needed or desired.

The compounds of formula (I) and the compounds of the formula (Ib) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) or a compound of the formula (Ib) and a suitable powder base such as lactose or starch.

Alternatively, the compounds of the formula (I) and the compounds of the formula (Ib) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the formula (I) and the compounds of the formula (Ib) may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the pulmonary or rectal routes.

They may also be administered by the ocular route. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of the formula (I) and the compounds of the formula (Ib) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the formula (I) and the compounds of the formula (Ib) may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

Oral administration is preferred.

Included within the scope of the present invention are embodiments comprising the co-administration of a compound of the present invention with one or more additional therapeutic agents, and compositions containing a compound of the present invention along with one or more additional therapeutic agents. Such a combination therapy is especially useful for the treatment of infection by HIV and related retroviruses which may evolve rapidly into strains resistant to any monotherapy. Alternatively, additional therapeutic agents may be desirable to treat diseases and conditions which result from or accompany the disease being treated with the compound of the present invention. For example, in the treatment of an HIV or related retroviral infection, it may be desirable to additionally treat opportunistic infections, neoplasms and other conditions which occur as a result of the immuno-compromised state of the patient being treated.

Preferred combinations of the present invention include simultaneous or sequential treatment with a compound of the formula (I) or a compound of the formula (Ib), as defined above, or a pharmaceutically acceptable salt thereof, and:

(a) one or more reverse transcriptase inhibitors such as zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, adefovir, combivir or trizivir;
(b) one or more non-nucleoside reverse transcriptase inhibitors such as nevirapine, delavirdine or efavirenz;
(c) one or more HIV protease inhibitors such as indanivir, ritonavir, saquinavir or nelfinavir;
(d) one or more CCR5 antagonists such as TAK-779 or SCH-351125;
(e) one or more CXCR4 antagonists such as AMD-3100;
(f) one or more integrase inhibitors;
(g) one or more inhibitors of viral fusion such as T-20 or T-1249;
(h) one or more investigational drugs such as KNI-272, amprenavir, GW-33908, FTC, PMPA, S-1153, MKC-442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378, KNI-764, DPC-083, TMC-120 or TMC-125; or
(i) one or more antifungal or antibacterial agents such as fluconazole.

The activity of the compounds of the invention as reverse transcriptase inhibitors and as agents for treating HIV infections may be measured using the following assays.

A. Inhibition of HIV-1 reverse transcriptase enzyme

The reverse transcriptase activity of the compounds of the invention may be assayed as following. Using the purified recombinant HIV-1 reverse transcriptase (RT, EC, 2.7.7.49) obtained by expression in Escherichia Coli, a 96-well plate assay system was established for assaying a large number of samples using either the Poly(rA)-oligo(dT) Reverse Transcriptase [3H]-SPA enzyme assay system (Amersham NK9020) or the [3H]-flashplate enzyme assay system (NEN - SMP 103) and following the manufacturer's recommendations. The compounds were dissolved in 100% DMSO and diluted with the appropriate buffer to a 5% final DMSO concentration. The inhibitory activity was expressed in percent inhibition relative to the DMSO control. The concentration at which the compound inhibited the reverse transcriptase by 50% was expressed as the IC_{50} of the compound.

B. Anti-Human Immunodeficiency Virus (HIV-1) cell culture assay

The anti-HIV activity of the compounds of the invention may be assayed by the following procedures.

1) SupT1 cells were cultured in an RPMI-1640 medium supplemented with 10% foetal calf serum and were split so that they were in growth phase on the day of use.

2) The compounds were dissolved in 100% DMSO and diluted with the above culture medium to predetermined concentrations and distributed in 20µl aliquots into a 96-well microtiter plate (0.1% DMSO final concentration).

3) To prepare infected cells, 100µl of RF viruses (TCID50 of 10^7/ml) were added to 10^6 cells and incubated for 1 hour at 37°C. The cells were then washed twice in PBS and resuspended in the culture medium at a density of 2.2 $\times 10^5$cells/ml.

180µl of these infected cells was transferred to wells of the 96 well plate containing the compounds.

4) The plate was incubated in a CO_2 incubator at 37°C for 4 days. The cell survival rates were measured following the manufacturer's recommendations (CellTiter 96® AQ_{ueous} Non-Radioactive Assay - Promega (cat no: G5430)). The concentration at which the compound inhibited the cytotoxic effect of the virus by 50% was expressed as the EC_{50}.

Thus the invention provides:

(i) the use of a compound of the formula (I) or a compound of the formula (Ib) or a pharmaceutically acceptable salt or solvate of either in the manufacture of a reverse transcriptase inhibitor or modulator;

(ii) the use of a compound of the formula (I) or a compound of the formula (Ib), or a pharmaceutically acceptable salt or solvate of either in the manufacture of a medicament for the treatment of a human immunodeficiency viral (HIV), or genetically related retroviral, infection or a resulting acquired immunodeficiency syndrome (AIDS);

(iii) a compound of the formula (I) or a compound of the formula (Ib), or a pharmaceutically acceptable salt or solvate of either, for use as a reverse transcriptase inhibitor;

(iv) a compound of the formula (I) or a compound of the formula (Ib) or a pharmaceutically acceptable salt or solvate of either, for use in the treatment of a human immunodeficiency viral (HIV), or genetically related retroviral, infection or a resulting acquired immunodeficiency syndrome (AIDS);

(v) a method of treatment or prevention of a disorder treatable by the inhibition of reverse transcriptase, comprising the administration of an effective amount of a compound of the formula (I) or a compound of the formula (Ib), or a pharmaceutically acceptable salt or solvate of either, to a patient in need of such treatment;

(vi) a method of treatment of a human immunodeficiency viral (HIV), or genetically related retroviral, infection or a resulting acquired immunodeficiency syndrome (AIDS) comprising the administration of an effective amount of a compound of the formula (I) or a compound of the formula (Ib), or a pharmaceutically acceptable salt or solvate of either, to a patient in need of such treatment;

(vii) a compound of the formula (Ib) or a pharmaceutically acceptable salt or solvate thereof;

(viii) a process for the preparation of a compound of the formula (Ib) or a pharmaceutically acceptable salt or solvate thereof;

(ix) a pharmaceutical composition including a compound of the formula (Ib) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

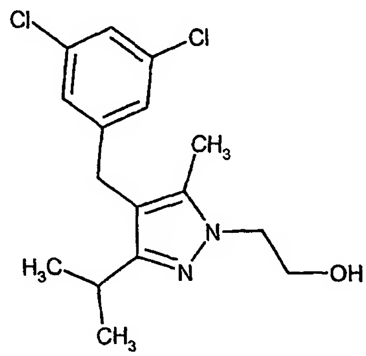
(x) a compound of the formula (Ib) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

The following Examples illustrate the preparation of the compounds of the formula (I) and the compounds of the formula (Ib). The synthesis of certain intermediates used therein are described in the Preparations section that follows the Examples.

^{1}H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used: HRMS, high resolution mass spectrometry; hplc, high performance liquid chromatography; nOe, nuclear Overhauser effect; m.p., melting point; h, hour; Et, ethyl; $CDCl_3$, deuterochloroform; D_6-DMSO, deuterodimethylsulphoxide; CD_3OD, deuteromethanol; THF, tetrahydrofuran. '0.880 Ammonia solution' means a concentrated aqueous solution of ammonia having a specific gravity of 0.88. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F_{254} plates, R_f is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate. In certain of the Examples there is the possibility of regioisomerism in the product. The structures of certain Examples, for instance Examples 7 and 13 have been proven by nOe experiments. The regiochemistry of other Examples has been assigned by comparing characteristic shifts in their NMR spectra with the corresponding shifts in the NMR spectra of Examples 7 and 13.

EXAMPLE 1

2-[4-(3,5-Dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]ethanol

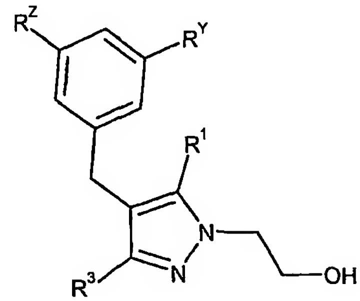


A solution of the ester of Example 7 (170mg, 0.46mmol) in dry ether (3.5ml) was added to a suspension of lithium aluminium hydride (17.5mg, 0.46mmol) in dry ether (2ml) cooled to -78°C under nitrogen. After stirring at -78°C for 1hour and at 0°C for 1hour the reaction was quenched with water (5ml) and then partitioned between ether (30ml) and aqueous hydrochloric acid solution (pH=3, 30ml) and the aqueous layer was further extracted with ether (2x30ml). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (2:1, by volume) to provide the title compound (116.3mg) as a white solid, m.p. 77-78°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.18 (d, 6H), 2.08 (s, 3H), 2.80 (heptet, 1H), 3.75 (s, 2H), 4.00 (m, 2H), 4.06 (m, 2H), 4.19 (t, 1H), 6.97 (s, 2H), 7.18 (s, 1H).
HRMS (electrospray): m/z [MH^+] 327.1026 (calculated 327.1026).

EXAMPLES 2 TO 6

The compounds of the following tabulated examples of the general formula:



were prepared by a similar method to that of Example 1 using the appropriate esters.

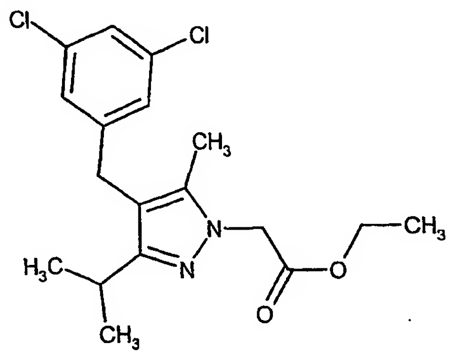
Example No.	R^3	R^1	R^Z	R^Y	LRMS m/z =	Analytical data, starting ester and variations in procedure.
2	CH_3CH_2-	CH_3CH_2-	Cl	Cl	(thermospray): 327 [MH^+]	^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.06 (t, 3H), 1.18 (t, 3H), 2.50 (m, 4H), 3.72 (s, 2H), 4.05 (m, 2H), 4.12 (m, 2H), 4.19 (br. t, 1H), 6.99 (s, 2H), 7.19 (s, 1H). Contains *ca.* 10% monodechlorinated impurity as judged by LCMS (50x2mm Magellen 3 micron C18 column, solvent gradient 0.1%, by volume aqueous formic acid:0.1%, by volume formic acid in acetonitrile (95:5, by volume) to 0.1%, by volume aqueous formic acid:0.1%, by volume formic acid in acetonitrile (5:95, by volume), electrospray MS). Ester of Example 9. Chromatography with a solvent gradient of toluene:ethyl acetate (1:1, by volume) then toluene:ethyl acetate (1:2, by volume).
3	$CH_3CH(CH_3)$-	CH_3-	Cl	H	(thermospray):	^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (d, 6H), 2.06 (s, 3H), 2.82 (m, 1H), 3.73 (s, 2H), 3.99 (m, 2H), 4.06 (m,

					293 [MH^+]	2H), 4.29 (br. s, 1H), 6.96 (m, 1H), 7.05 (s, 1H), 7.15 (m, 2H). Microanalysis: Found: C, 65.58; H, 7.30; N, 9.33. $C_{16}H_{21}ClN_2O$ requires C, 65.63; H, 7.23; N, 9.57%. Ester of Example 15. Chromatography with a solvent gradient of pentane:ethyl acetate (2:1, by volume) then pentane:ethyl acetate (1:1, by volume).
4	$CH_3CH(CH_3)$-	CH_3-	F	F	(electrospray): 295 [MH^+]	^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (d, 6H), 2.10 (s, 3H), 2.80 (heptet, 1H), 3.74 (s, 2H), 4.00 (m, 2H), 4.06 (m, 2H), 4.20 (t, 1H), 6.60 (m, 3H). Ester of Example 16. Chromatography with a solvent gradient of pentane:ethyl acetate (2:1, by volume) then pentane:ethyl acetate (1:1, by volume).
5	$CH_3CH(CH_3)$-	CH_3-	F	H	(thermospray): 277 [MH^+]	^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.18 (d, 6H), 2.08 (s, 3H), 2.84 (heptet, 1H), 3.76 (s, 2H), 3.98 (m, 2H), 4.05 (m, 2H), 4.23 (t, 1H), 6.75 (d, 1H), 6.86 (m, 2H), 7.20 (m, 1H).

						Microanalysis: Found: C, 69.45; H, 7.71; N, 9.96. $C_{16}H_{21}FN_2O$ requires C, 69.54; H, 7.66; N, 10.14%. Ester of Example 10. Chromatography with pentane:ethyl acetate (1:1, by volume).
6	CH_3-	$CH_3CH(CH_3)$-	Cl	Cl	(thermospray): 327 [MH^+]	^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (d, 6H), 2.06 (s, 3H), 3.06 (heptet,1H), 3.79 (s, 2H), 4.00 (m, 2H), 4.13 (m, 2H), 6.95 (s, 2H), 7.18 (s, 1H). HRMS (electrospray): m/z [MH^+] 327.1031 (calculated 327.1026). Ester of Example 8, using Method B Chromatography with a solvent gradient of pentane:ethyl acetate (1:1, by volume) then ethyl acetate.

EXAMPLES 7 AND 8

Ethyl [4-(3,5-dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate (Example 7)



Method A:

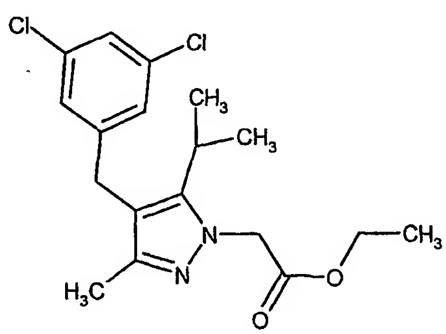
A solution of 21% weight/volume sodium ethoxide in ethanol (227µL, 0.7mmol) was added dropwise to a stirred solution of the pyrazole of Example 17 (172.7mg, 0.61mmol) in dry ethanol (1ml) at room temperature in a Reacti-vial (Trade Mark) (a sealable reaction vessel; available from Pierce & Warriner (UK) Ltd). Ethyl bromoacetate (136µL, 1.22mmol) was added and the Reacti-vial (Trade Mark) was sealed and heated at 80°C for 2 hours and then stirred at room temperature for 16 hours. Further sodium ethoxide in ethanol (227µL, 0.7mmol) and ethyl bromoacetate (136µL, 1.22mmol) were added and the sealed mixture was heated for a further 7 hours. After cooling to room temperature further sodium ethoxide in ethanol (227µL, 0.7mmol) and ethyl bromoacetate (136µL, 1.22mmol) were added and the sealed mixture was heated for a further 10 hours. After cooling to room temperature the mixture was concentrated under reduced pressure and the residue was partitioned between water (30ml) and dichloromethane (30ml) and the aqueous layer was further extracted with dichloromethane (2x30ml). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure and the crude product (321mg) was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (7:1, by volume) to provide Example 7 (175.3mg) as a white solid, m.p. 90-92°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.18 (d, 6H), 1.27 (t, 3H), 2.06 (s, 3H), 2.81 (heptet, 1H), 3.74 (s, 2H), 4.22 (q, 2H), 4.83 (s, 2H), 6.96 (s, 2H), 7.17 (s, 1H). This structure was confirmed by nOe experiments.
HRMS (electrospray): m/z [MH^+] 369.1135 (calculated 369.1131).

Method B:

A solution of the β-diketone of Preparation 1 (245mg, 0.85mmol), ethyl hydrazinoacetate hydrochloride (132mg, 0.85mmol) and triethylamine (131μL, 0.94mmol) in ethanol (1ml) was stirred and heated in a sealed Reacti-vial (Trade Mark) at 80°C for 24 hours. After cooling the mixture was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (10:1, by volume) then pentane:ethyl acetate (5:1, by volume) to provide Example 7 (28.6mg) as a white solid, m.p. 94-95°C.

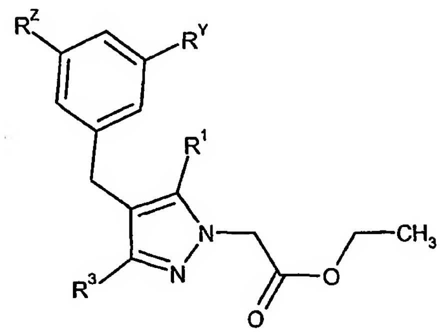
Further elution of the column afforded ethyl [4-(3,5-dichlorobenzyl)-5-isopropyl-3-methyl-1*H*-pyrazol-1-yl]acetate (Example 8) (228.8mg) as a yellow oil.



^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.19 (d, 6H), 1.28 (t, 3H), 2.06 (s, 3H), 2.92 (heptet, 1H), 3.82 (s, 2H), 4.23 (q, 2H), 4.86 (s, 2H), 6.96 (s, 2H), 7.17 (s, 1H). This structure was confirmed by nOe experiments.
HRMS (electrospray): m/z [MH^+] 369.1134 (calculated 369.1131).

EXAMPLES 9 TO 10

The compounds of the following tabulated Examples of the general formula:



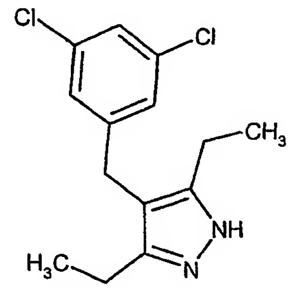
were prepared by a similar method to that of Example 7, Method A using the appropriate pyrazole.

Example No.	R^3	R^1	R^Z	R^Y	LRMS m/z =	Analytical data, starting pyrazole and variations in procedure.
9	CH_3CH_2-	CH_3CH_2-	Cl	Cl	(thermospray): 369 [MH^+]	^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.14 (t, 3H), 1.16 (t, 3H), 1.28 (t, 3H), 2.48 (m, 4H), 3.75 (s, 2H), 4.24 (q, 2H), 4.84 (s, 2H), 6.99 (s, 2H), 7.19 (s, 1H). Pyrazole of Example 11. Microanalysis: Found: C, 58.41; H, 5.95; N, 7.39. $C_{18}H_{22}Cl_2N_2O_2$ requires C, 58.54; H, 6.00; N, 7.59%. Contains *ca.* 10% monodechlorinated impurity as judged by LCMS. Chromatography with a solvent gradient of dichloromethane then dichloromethane:methanol (99:1, by volume).
10	$CH_3CH(CH_3)$-	CH_3-	F	H	(thermospray): 319 [MH^+]	^{1}H-NMR (400MHz, $CDCl_3$): δ =1.13 (d, 6H), 1.23 (t, 3H), 2.03 (s, 3H), 2.80 (heptet, 1H), 3.75 (s, 2H), 4.20 (q, 2H), 4.80 (s, 2H), 6.71 (d, 1H), 6.85 (m, 2H), 7.16 (m, 1H). HRMS (electrospray): m/z [MH^+] 319.1814 (calculated

						319.1817). Pyrazole of Example 19. Chromatography with pentane:ethyl acetate (5:1, by volume).

EXAMPLE 11

4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazole



Hydrazine hydrate (187μL, 3.85mmol) was added to a stirred solution of the β-diketone of Preparation 5 (1.00g, 3.5mmol) in ethanol (2.5ml) in a Reacti-vial (Trade Mark) at room temperature. The Reacti-vial (Trade Mark) was sealed and the mixture heated at 100°C for 3 hours. After cooling to room temperature the mixture was concentrated under reduced pressure to leave an oily white solid (1g) which was purified by flash chromatography on silica gel eluting with dichlormethane:methanol (98:2, by volume) to give the crude product which was recrystallised from diisopropylether (10ml) to give the title compound (150mg) as a white solid. LCMS analysis revealed a small amount (*ca.*10%) of monodechlorinated impurity carried through of Preparation 5. This impurity could be removed by hplc (150x21.2mm Phenomenonex Luna C_{18} 5 micron column, solvent gradient 0.1%,by volume aqueous diethylamine:methanol (90:10, by volume) to 0.1%,by volume aqueous diethylamine:methanol (10:90, by volume)) to afford pure title compound.

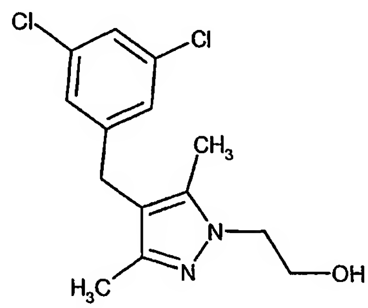
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.20 (t, 6H), 2.55 (q, 4H), 3.73 (s, 2H), 6.99 (s, 2H), 7.19 (s, 1H).

LRMS (thermospray): m/z [MH^+] 283.

Microanalysis: Found: C, 59.53; H, 5.71; N, 9.82. $C_{14}H_{16}Cl_2N_2$ requires C, 59.38; H, 5.69; N, 9.89%.

EXAMPLE 12

2-[4-(3,5-Dichlorobenzyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethanol



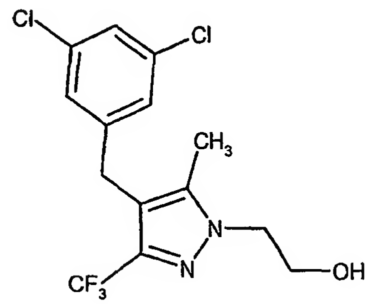
To a stirred suspension of the diketone of Preparation 4 (302mg, 1.17mmol) in ethanol (1ml) was added 2-hydroxyethyl hydrazine (81µL, 1.29mmol) and the resulting mixture was heated at 100°C in a sealed Reacti-vial (Trade Mark) for 6 hours. After cooling, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (1:2, by volume) then pentane:ethyl acetate (1:5, by volume) to afford the title compound (351mg) as a white powder.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.08 (s, 3H), 2.11 (s, 3H), 3.62 (br. m, 1H), 3.66 (s, 2H), 4.00 (m, 2H), 4.07 (m, 2H), 6.95 (s, 2H), 7.16 (s, 1H).
LRMS (thermospray): m/z [MH^+] 299.
Microanalysis: Found: C, 56.15; H, 5.38; N, 9.27. $C_{14}H_{16}Cl_2N_2O$ requires C, 56.20; H, 5.39; N, 9.36%.

LCMS analysis revealed a small amount (<10%) of dechlorinated impurities presumably arising from the reduction step in Preparation 4 but not detected at that stage. A portion of the product (190mg) was recrystallised from ethanol:water (2:1, by volume) (3ml) to afford a white solid (150mg). LCMS analysis then revealed only a trace amount (<5%) of mono-chlorinated product. This over reduction could probably be avoided by using the alternative reduction procedure of Preparation 6.

EXAMPLE 13

2-[4-(3,5-Dichlorobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol



A solution of the diketone of Preparation 6 (76mg, 0.243mmol) in ethanol (2ml) was added to 2-hydroxethyl hydrazine (18μL, 0.267mmol) and the resulting mixture was heated at 90°C in a sealed Reacti-vial (Trade Mark) for 2 hours. After cooling the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane then dichloromethane:methanol (99:1, by volume) to afford the title compound (62mg) as an off-white solid, m.p. 91-93°C.

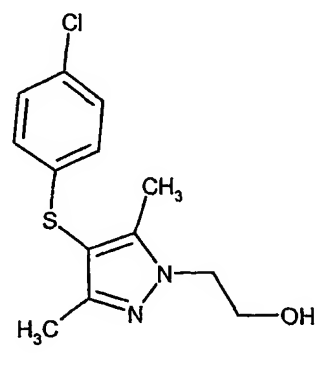
^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.13 (s, 3H), 2.61 (m, 1H), 3.80 (s, 2H), 4.05 (m, 2H), 4.17 (m, 2H), 6.92 (s, 2H), 7.16 (s, 1H). This structure was confirmed by nOe experiments.

LRMS (thermospray): m/z [MH^+] 353.

Microanalysis: Found: C, 47.66; H, 3.75; N, 7.78. $C_{14}H_{13}Cl_2F_3N_2O$ requires C, 47.61; H, 3.71; N, 7.93%.

EXAMPLE 14

2-{4-[(4-Chlorophenyl)sulfanyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol



The title compound was prepared by a similar method to that of Example 13 using 3-(4-chlorophenylthio)pentane-2,4-dione except that the crude product was purified by recrystallisation from diisopropylether (*ca.* 25ml) to give pale yellow crystals, m.p. 88.9-90.3°C

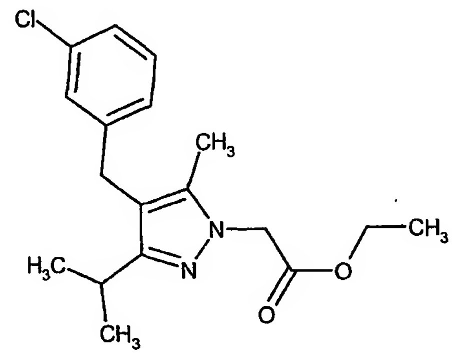
^{1}H-NMR 300MHz, $CDCl_3$): δ = 2.20 (s, 3H), 2.29 (s, 3H), 4.04 (t, 2H), 4.12 (t, 2H), 6.90 (d, 2H), 7.18 (d, 2H).

LRMS (thermospray): m/z [MH^+] 282.

Microanalysis: Found: C, 54.92; H, 5.39; N, 9.91. $C_{13}H_{15}ClN_2OS$ requires C, 55.22; H, 5.35; N, 9.91%.

EXAMPLE 15

Ethyl [4-(3-chlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate



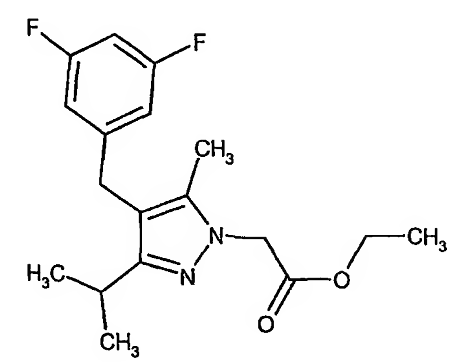
The title compound was prepared by a method similar to that of Example 7, Method A using the pyrazole of Example 20, and was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (5:1, by volume) and was obtained as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.13 (d, 6H), 1.26 (t, 3H), 2.03 (s, 3H), 2.79 (m, 1H), 3.72 (s, 2H), 4.19 (q, 2H), 4.81 (s, 2H), 6.93 (m, 1H), 7.03 (s, 1H), 7.11 (m, 2H).

LRMS (thermospray): m/z [MH^+] 335.

EXAMPLE 16

Ethyl [4-(3,5-difluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate

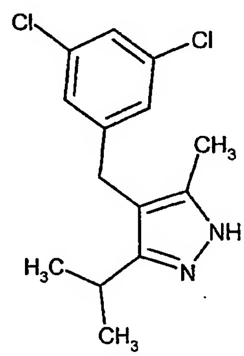


The title compound was prepared by a method similar to that of Example 7, Method A using the pyrazole of Example 18 and was obtained as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.16 (d, 6H), 1.27 (t, 3H), 2.06 (s, 3H), 2.82 (heptet, 1H), 3.76 (s, 2H), 4.23 (q, 2H), 4.84 (s, 2H), 6.60 (m, 3H).
HRMS (electrospray): m/z [MH^+] 337.1719 (calculated 337.1722).

EXAMPLE 17

4-(3,5-Dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole

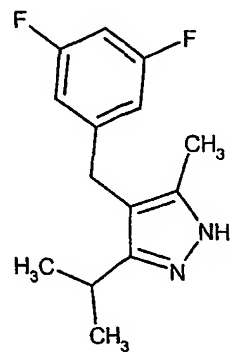


Hydrazine hydrate (50.1mg, 1mmol) was added dropwise to a stirred solution of the β-diketone of Preparation 1 (287.2mg, 1mmol) in dry ethanol (1ml) in a Reacti-vial (Trade Mark) at RT. The Reacti-vial (Trade Mark) was sealed and the mixture heated at 80°C for 24 hours. After cooling to room temperature the mixture was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (3:1, by volume) then pentane:ethyl acetate (2:1, by volume) to afford the title compound (225.6mg) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.10 (d, 6H), 2.11 (s, 3H), 2.89 (heptet, 1H), 3.74 (s, 2H), 6.97 (s, 2H), 7.18 (s, 1H).
LRMS (electrospray): m/z [MH^+] 285.

EXAMPLE 18

4-(3,5-Difluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole

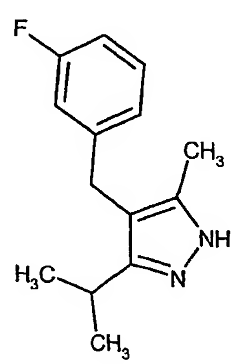


The title compound was prepared by a method similar to that of Example 17 using the β-diketone of Preparation 2 and was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (2:1, by volume) to afford the title compound as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.16 (d, 6H), 2.08 (s, 3H), 2.85 (heptet, 1H), 3.71 (s, 2H), 6.58 (m, 3H).
LRMS (thermospray): m/z [MH^+] 251.

EXAMPLE 19

4-(3-Fluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole



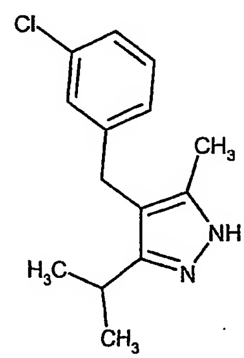
The title compound was prepared by a method similar to that of Example 17 using the β-diketone of Preparation 3 and was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (3:1, by

volume) then pentane:ethyl acetate (2:1, by volume) to afford the title compound as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.22 (d, 6H), 2.11 (s, 3H), 2.90 (heptet, 1H), 3.77 (s, 2H), 6.77 (d, 1H), 6.89 (m, 2H), 7.20 (m, 1H).
LRMS (thermospray): m/z [MH^+] 233.

EXAMPLE 20

4-(3-Chlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole

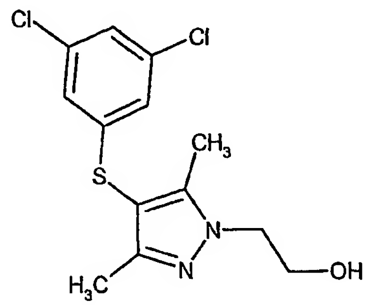


The title compound was prepared by a method similar to that of Example 11 using the β-diketone of Preparation 7 and was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (5:1, by volume) then pentane:ethyl acetate (3:1, by volume) to afford the title compound as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.19 (d, 6H), 2.10 (s, 3H), 2.84-2.97 (m, 1H), 3.74 (s, 2H), 6.94-6.99 (m, 1H), 7.06 (s, 1H), 7.11-7.21 (m, 2H).
LRMS (thermospray): m/z [MH^+] 249.

EXAMPLE 21

2-{4-[(3,5-Dichlorophenyl)sulfanyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol

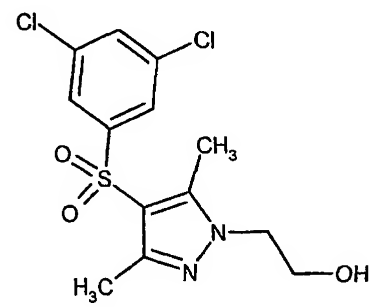


The β-diketone of Preparation 15 (750mg, 2.71mmol) was added to a stirred solution of 2-hydroxyethyl hydrazine (202μL, 2.98mmol) in ethanol (27ml) at room temperature under nitrogen and the resulting yellow solution was heated under reflux for 22 hours. After cooling the mixture was concentrated under reduced pressure and the resulting pale yellow solid was purified by flash chromatography on silica gel eluting with methanol:dichloromethane (2:98, by volume) to provide the title compound (729mg) as a white powder, m.p. 118-120°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.18 (s, 3H), 2.24 (s, 3H), 3.19 (t, 1H), 4.01 (m, 2H), 4.12 (m, 2H), 6.78 (s, 2H), 7.02 (s, 1H).
LRMS (thermospray): m/z [MH^+] 317.
Microanalysis: Found: C, 49.13; H, 4.45; N, 8.59. $C_{13}H_{14}Cl_2N_2OS$ requires C, 49.22; H, 4.45; N, 8.83%.

EXAMPLE 22

2-{4-[(3,5-Dichlorophenyl)sulfonyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol

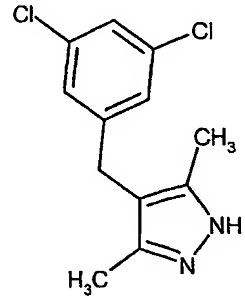


A solution of Oxone (Trade Mark) (581mg, 0.946mmol) in water was added to a stirred suspension of the sulphide of Example 21 (200mg, 0.63mmol) in methanol (2.5ml) at 0°C producing a viscous white suspension. The cooling bath was removed and further methanol (2.5ml) was added to aid dissolution and stirring. The mixture was stirred at room temperature for 2½ hours and at 50°C for 24 hours. After cooling the mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (50ml) and water (25ml). The organic layer was washed with brine (25ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a white solid (195mg). The crude product was pre-absorbed on silica gel and purified by flash chromatography on silica gel eluting with methanol:dichloromethane (2:98, by volume) to provide the title compound (175mg) as a white solid, m.p. 199-200°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.51 (s, 3H), 2.70 (s, 1H), 3.99 (m, 2H), 4.05 (m, 2H), 7.51 (s, 1H), 7.70 (s, 2H).
LRMS (thermospray): m/z [MH^+] 349.
Microanalysis: Found: C, 44.62; H, 4.03; N, 7.96. $C_{13}H_{14}Cl_2N_2O_3S$ requires C, 44.71; H, 4.04; N, 8.02%.

EXAMPLE 23

4-(3,5-Dichlorobenzyl)-3,5-dimethyl-1*H*-pyrazole



A stirred suspension of the β-diketone of Preparation 4 (1.01g, 3.90mmol) in ethanol (3ml) was treated with hydrazine hydrate (208μL, 4.29mmol) and the resulting mixture was heated at 100°C in a sealed Reacti-vial (Trade Mark) for 3 hours. After cooling, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with methanol:dichloromethane (2:98, by volume) and then methanol:dichloromethane (5:95, by volume) to afford the title compound (485mg) as a pale yellow solid, m.p. 133-134°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.18 (s, 6H), 2.69 (s, 2H), 6.98 (s, 2H), 7.18 (s, 1H).

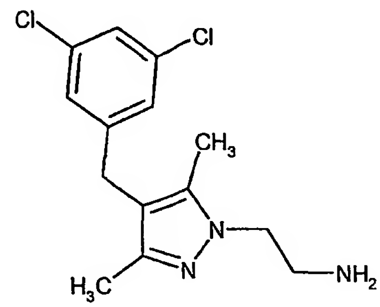
LRMS (electrospray): m/z [MH^+] 255.

Microanalysis: Found: C, 56.72; H, 4.79; N, 10.90. $C_{12}H_{12}Cl_2N_2$ requires C, 56.49; H, 4.74; N, 10.98%.

LCMS analysis of the product revealed a small amount (<20%) of dechlorinated impurities presumably arising from the reduction step in Preparation 4 but not detected at that stage. This over-reduction could be avoided by using the alternative reduction procedure of Preparation 6.

EXAMPLE 24

2-[4-(3,5-Dichlorobenzyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethanamine

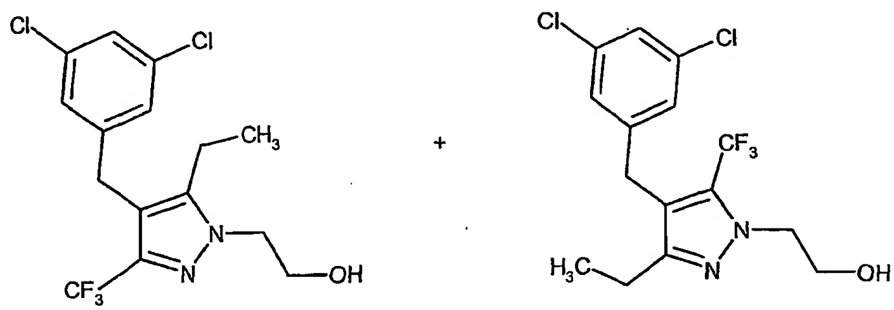


A stirred suspension of the pyrazole (200mg, 0.78mmol) of Example 23 and 2-chloroethylamine hydrochloride (136mg, 1.18mmol) in toluene (1ml) was heated at 120°C in a sealed Reacti-vial (Trade Mark) for 18 hours. After cooling, the mixture was diluted with dichloromethane (30ml), washed with 2M aqueous sodium hydroxide solution (20ml), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with methanol:dichloromethane:ammonia (5:95:0.5, by volume) to afford the title compound (45mg) as white crystals, m.p. 70-72°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.08 (s, 3H), 2.13 (s, 3H), 3.08 (t, 2H), 3.62 (s, 2H), 4.02 (t, 2H), 6.95 (s, 2H), 7.17 (s, 1H).
LRMS (electrospray): m/z [MH^+] 298.

EXAMPLES 25 AND 26

2-[4-(3,5-Dichlorobenzyl)-5-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol (Example 25) and 2-[4-(3,5-Dichlorobenzyl)-3-ethyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol (Example 26)



A solution of the β-diketone of Preparation 17 (180mg, 0.55mmol) in ethanol (5ml) was treated with 2-hydroxyethyl hydrazine (41μL, 0.61mmol) and heated at 90°C in a sealed Reacti-vial (Trade Mark) for 5 hours. After cooling, the mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a solvent gradient of methanol:dichloromethane (0:100, by volume) then methanol:dichloromethane (0.5:99.5, by volume). The less polar product to elute from the column was 2-[4-(3,5-Dichlorobenzyl)-5-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol isolated as a colourless oil (40mg), which solidified on standing, m.p. 70-72°C.

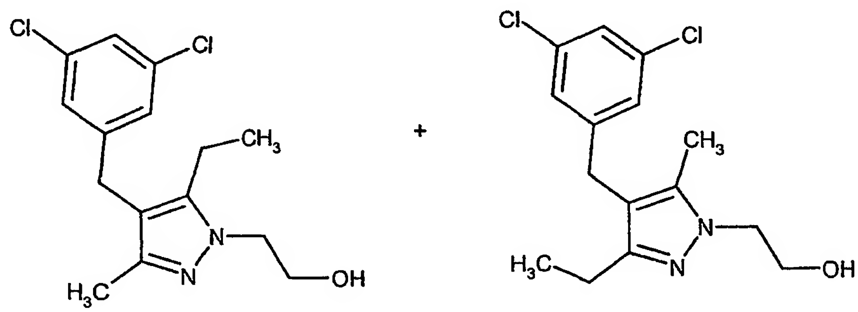
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.03 (t, 3H), 2.60 (q, 2H), 2.90 (t, 1H), 3.87 (s, 2H), 4.13 (m, 2H), 4.20 (m, 2H), 7.00 (s, 2H), 7.20 (s, 1H).
LRMS (thermospray): m/z [MH^+] 367.
Microanalysis: Found: C, 48.86; H, 4.07; N, 7.45. $C_{15}H_{15}Cl_2F_3N_2O$ requires C, 49.07; H, 4.12; N, 7.43%.

The more polar product to elute from the column was further purified by flash chromatography on silica gel eluting with a solvent gradient of acetonitrile:dichloromethane (5:95, by volume) then acetonitrile:dichloromethane (10:90, by volume). 2-[4-(3,5-Dichlorobenzyl)-3-ethyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol was isolated as a colourless oil (10mg).

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.17 (t, 3H), 2.52 (q, 2H), 3.48 (brs, 1H), 3.87 (s, 2H), 4.10 (s, 2H), 4.32 (s, 2H), 6.94 (s, 2H), 7.20 (s, 1H).
LRMS (thermospray): m/z [MH$^+$] 367.

EXAMPLES 27 AND 28

2-[4-(3,5-Dichlorobenzyl)-5-ethyl-3-methyl-1*H*-pyrazol-1-yl]ethanol (Example 27) and 2-[4-(3,5-Dichlorobenzyl)-3-ethyl-5-methyl-1*H*-pyrazol-1-yl]ethanol (Example 28)



A solution of the β-diketone of Preparation 20 (300mg, 1.10mmol) in ethanol (5ml) was treated with 2-hydroxyethyl hydrazine (81μL, 1.20mmol) and heated at 90°C for 18 hours. After cooling, the mixture was concentrated under reduced pressure. The two isomers were separated by HPLC (Chiracel OD 25cm x 2cm column; mobile phase, by volume: 80% hexane, 20% iso-propyl alcohol; flow rate: 10 ml/min). The major isomer was isolated as a white solid (60mg, retention time 12.4 minutes), m.p. 106-107°C and shown to be 2-[4-(3,5-dichlorobenzyl)-5-ethyl-3-methyl-1*H*-pyrazol-1-yl]ethanol by nOe experiments.

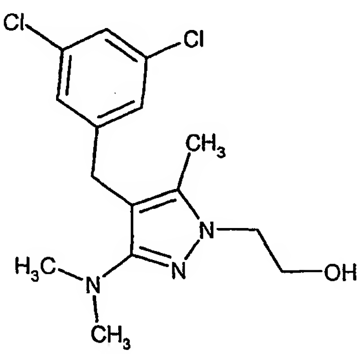
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.06 (t, 3H), 2.10 (s, 3H), 2.55 (q, 2H), 3.71 (s, 2H), 4.03 (s, 2H), 4.10 (s, 2H), 6.98 (s, 2H), 7.20 (s, 1H).
LRMS (thermospray): m/z [MH$^+$] 313.

The minor isomer was shown to be 2-[4-(3,5-Dichlorobenzyl)-3-ethyl-5-methyl-1*H*-pyrazol-1-yl]ethanol and isolated as a white solid (10mg, retention time 10.0 minutes), m.p. 100-101°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.16 (t, 3H), 2.16 (s, 3H), 2.52 (q, 2H), 3.74 (s, 2H), 4.03 (s, 2H), 4.13 (s, 2H), 6.98 (s, 2H), 7.20 (s, 1H).
LRMS (thermospray): m/z [MH^+] 313.

EXAMPLE 29

2-[4-(3,5-Dichlorobenzyl)-3-(dimethylamino)-5-methyl-1*H*-pyrazol-1-yl]ethanol

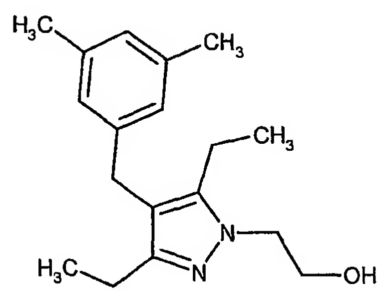


A solution of the amine of Example 87 (18mg, 0.06mmol) in dichloromethane (0.3ml) was treated with triethylamine (8.0μL, 0.06mmol) followed by paraformaldehyde (4.0mg, 0.13mmol) and stirred at room temperature for 1 hour. Acetic acid was added (3.5μL, 0.06mmol) and after a further hour sodium triacteoxyborohydride (19mg, 0.09mmol) was added and the reaction mixture was stirred at room temperature for 18 hours. Further paraformaldehyde (2.2eq) and sodium triacteoxyborohydride (1.5eq) were added and the reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was diluted with dichloromethane (10ml) and washed with 10% aqueous potassium carbonate solution (10ml). The organic extract was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (98:2:0.5) to afford the title compound as a colourless oil (4.5mg).

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.08 (s, 3H), 2.70 (s, 6H), 3.78 (s, 2H), 4.00 (s, 4H), 4.19 (m, 1H), 7.02 (s, 2H), 7.20 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 346.

EXAMPLE 30

2-[4-(3,5-Dimethylbenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol

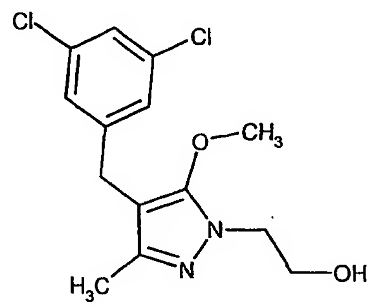


The title compound was prepared by a method similar to that of Example 25, using the β-diketone of Preparation 24. The crude material was purified by flash chromatography on silica gel eluting with methanol:dichloromethane (2:98, by volume) to afford the title compound as a yellow oil, which solidified on standing, m.p. 49.5-51.5°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.03 (t, 3H), 1.16 (t, 3H), 2.29 (s, 6H), 2.55 (m, 4H), 3.71 (s, 2H), 4.03 (m, 2H), 4.13 (m, 2H), 4.35 (brs, 1H), 6.77 (s, 2H), 6.84 (s, 1H).
LRMS (thermospray): m/z [MH^+] 287.

EXAMPLE 31

2-[4-(3,5-Dichlorobenzyl)-5-methoxy-3-methyl-1*H*-pyrazol-1-yl]ethanol



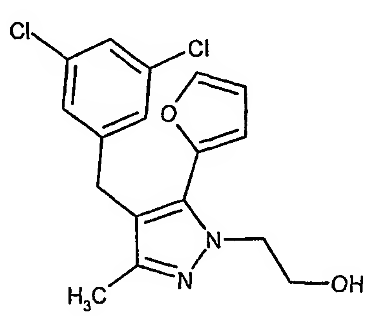
A solution of the ester of Example 88 (42mg, 0.12mmol) in tetrahydrofuran (2ml) at 0°C was treated dropwise with a solution of lithiumaluminiumhydride (1M in THF) and the resulting mixture was allowed to warm to room temperature and was stirred at this temperature for a further 30 minutes. The reaction mixture was diluted with ethyl acetate and washed with 1M aqueous sodium hydroxide solution and brine. The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford the title compound (34mg) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.07 (s, 3H), 3.45 (brs, 1H), 3.72 (s, 2H), 3.79 (s, 3H), 3.95 (m, 2H), 4.03 (m, 2H), 7.02 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH^+] 315.

EXAMPLE 32

2-[4-(3,5-Dichlorobenzyl)-5-(2-furyl)-3-methyl-1*H*-pyrazol-1-yl]ethanol



A solution of the β-diketone of Preparation 27 (1.0g, 3.20mmol) in ethanol (38ml) was treated with 2-hydroxyethyl hydrazine (239μL, 3.53mmol) and heated under reflux for 18 hours. After cooling, the reaction mixture was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (2:1, by volume) to afford the title compound as a yellow oil, which solidified on standing (703mg).

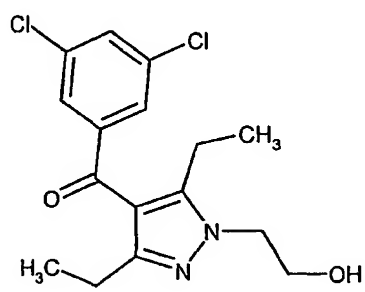
^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.16 (s, 3H), 3.58 (t, 1H), 3.80 (s, 2H), 4.01 (m, 2H), 4.28 (m, 2H), 6.37 (d, 1H), 6.49 (m, 1H), 6.99 (s, 2H), 7.18 (s, 1H), 7.36 (s, 1H).

LRMS (thermospray): m/z [MH^+] 351.

Microanalysis: Found: C, 58.12; H, 4.63; N, 7.84. $C_{17}H_{16}Cl_2N_2O_2$ requires C, 58.13; H, 4.59; N, 7.98%.

EXAMPLE 33

(3,5-Dichlorophenyl)[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]methanone

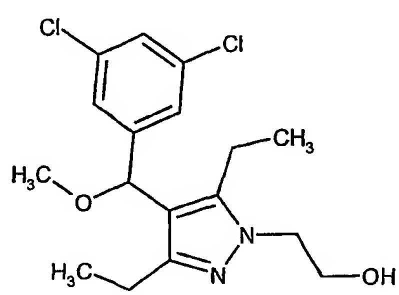


A solution of the protected alcohol of Preparation 32 (70mg, 0.15mmol) in tetrahydrofuran (1ml) was treated with tetrabutylammonium fluoride (1M in THF) (300μL, 0.30mmol), at room temperature, under a nitrogen atmosphere. After the reaction mixture had been stirred for 18 hours the solution was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (5:1, by volume) to afford the title compound (30mg) as a white solid, m.p. 133.5-134.4°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.13 (m, 6H), 2.52 (q, 2H), 2.74 (q, 2H), 3.65 (t, 1H), 4.10 (m, 2H), 4.19 (m, 2H), 7.61 (m, 3H).
LRMS (thermospray): m/z [MH^+] 341.
Microanalysis: Found: C, 56.03; H, 5.28; N, 8.13. $C_{16}H_{15}Cl_2N_2O_2$ requires C, 56.32; H, 5.32; N, 8.21%.

EXAMPLE 34

(±)-2-{4-[(3,5-Dichlorophenyl)(methoxy)methyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol



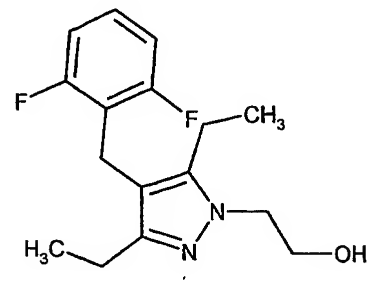
The title compound was prepared by a similar method to that of Example 33 using the protected alcohol of Preparation 33. The crude material was purified by flash chromatography on silica gel eluting with a solvent gradient of cyclohexane:ethyl acetate (5:1, by volume) gradually changing to cyclohexane:ethyl actetate (1:2, by volume) to afford the title compound as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.20 (t, 3H), 2.55 (m, 4H), 3.39 (s, 3H), 4.06 (m, 4H), 5.23 (s, 1H), 7.26 (m, 3H).

LRMS (thermospray): m/z [MH^+] 357.

EXAMPLE 35

2-[4-(2,6-Difluorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol



A mixture of the β-diketone of Preparation 35 (89mg, 0.35mmol), 2-hydroxyethyl hydrazine (24μL, 0.35mmol) and ethanol (350μL) was heated at 80°C in a sealed Reacti-vial (Trade Mark) for 18 hours. After cooling, the solution was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl actetate (2:1, by volume) to afford the title compound (67mg) as a white solid, m.p. 70-71°C.

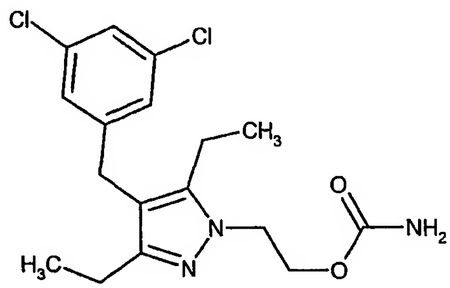
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.15 (t, 3H), 2.55 (q, 2H), 2.62 (q, 2H), 3.73 (s, 2H), 3.97 (m, 2H), 4.00 (m, 2H), 4.26 (t, 1H), 6.84 (t, 2H), 7.15 (m, 1H).

LRMS (electrospray): m/z [MH^+] 295.

Microanalysis: Found: C, 65.20; H, 6.87; N, 9.48. $C_{16}H_{20}F_2N_2O$ requires C, 65.29; H, 6.85; N, 9.52%.

EXAMPLE 36

2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl carbamate



A solution of the alcohol of Example 2 (50mg, 0.15mmol) in dichloromethane (1.5ml) was cooled to 0°C and treated dropwise with trichloroacetyl isocyanate (22µL, 0.18mmol) under a nitrogen atmosphere. After stirring at 0°C for 1.5 hours the solution was concentrated under reduced pressure. The residue was dissolved in methanol (1ml) and water (0.5ml) and cooled to 0°C. Potassium carbonate (64mg, 0.46mmol) was added and the resulting mixture was stirred at this temperature for 1 hour. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The solution was concentrated under reduced pressure. The residue was partitioned between dichloromethane and water. The organic extract was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to afford the title compound (42mg) as a white solid, m.p. 145-147°C.

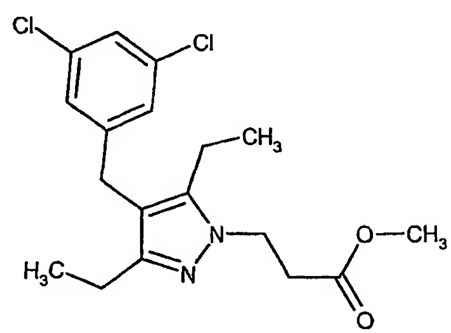
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.02 (t, 3H), 1.10 (t, 3H), 2.42 (m, 2H), 2.50 (m, 2H), 3.68 (s, 2H), 4.21 (t, 2H), 4.42 (t, 2H), 4.55 (brs, 2H), 6.94 (s, 2H), 7.15 (s, 1H).

LRMS (thermospray): m/z [MH^+] 370.

Microanalysis: Found: C, 54.95; H, 5.65; N, 11.20. $C_{17}H_{21}Cl_2N_3O_2$ requires C, 55.14; H, 5.72; N, 11.35%.

EXAMPLES 37 AND 38

Methyl 3-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]propanoate (Example 37)



A solution of the pyrazole of Example 11 (198mg, 0.70mmol) in ethanol (1ml) was treated with sodium ethoxide (21%$^{w}/_{v}$ in EtOH) (261μL, 0.81mmol) and then methyl-3-bromopropionate (153μL, 1.40mmol) and heated at 70°C in a sealed Reacti-vial (Trade Mark) for 18 hours. Over a period of 3 days more sodium ethoxide (2.65eq) and methyl-3-bromopropionate (6.0eq) were added and the reaction was maintained under the same conditions. After cooling, the solution was concentrated under reduced pressure. The residue was partitioned between dichloromethane and water. The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (5:1, by volume) to afford two products.

The first compound eluted off the column was ethyl 3-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]propanoate (Example 38) isolated as a pale yellow oil (150mg).

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.06 (t, 3H), 1.13 (t, 3H), 1.26 (t, 3H), 2.47 (q, 2H), 2.56 (q, 2H), 2.94 (t, 2H), 3.71 (s, 2H), 4.15 (q, 2H), 4.29 (t, 2H), 6.98 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH^+] 383.

Accurate Mass: Found: 383.1284 [MH^+]; $C_{19}H_{24}Cl_2N_2O_2$ requires 383.1288 [MH^+].

The second compound eluted was Example 37 (21mg) isolated as a colourless oil.

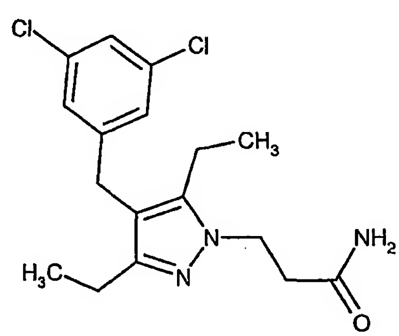
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.06 (t, 3H), 1.15 (t, 3H), 2.47 (q, 2H), 2.56 (q, 2H), 2.97 (t, 2H), 3.71 (s, 5H), 4.31 (t, 2H), 6.97 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH^+] 369.

Accurate Mass: Found: 369.1128 [MH^+]; $C_{18}H_{22}Cl_2N_2O_2$ requires 369.1131 [MH^+].

EXAMPLE 39

3-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]propanamide



A solution of the ethyl ester of Example 38 (60mg, 0.16mmol) in a saturated solution of ammonia in methanol (1.2ml) was heated at 90°C in a sealed Reacti-vial (Trade Mark) for 18 hours. Further saturated ammonia in methanol (1.0ml) was added and the reaction mixture was stirred at 90°C for 3 days. After cooling, the solution was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with ethyl acetate to afford the title compound (50mg) as a white solid, m.p. 140-142°C.

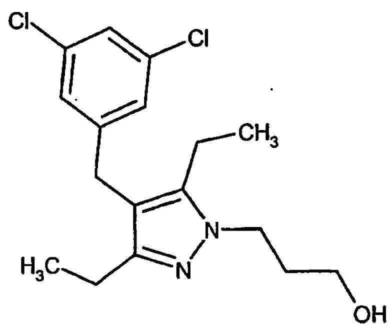
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.08 (t, 3H), 2.40 (q, 2H), 2.52 (q, 2H), 2.80 (t, 2H), 3.66 (s, 2H), 4.26 (t, 2H), 5.26 (brs, 1H), 6.29 (brs, 1H), 6.92 (s, 2H), 7.15 (s, 1H).

LRMS (electrospray): m/z [MH^+] 354.

Microanalysis: Found: C, 57.51; H, 6.01; N, 11.57. $C_{17}H_{21}Cl_2N_3O$ requires C, 57.63; H, 5.97; N, 11.86%.

EXAMPLE 40

3-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]-1-propanol



A solution of the ethyl ester of Example 38 (60mg, 0.16mmol) in diethyl ether (2ml) was cooled to -78°C, treated dropwise with lithium aluminium hydride (1M in THF) (170µL, 0.17mmol) and stirred at -78°C, under a nitrogen atmosphere for 30 minutes. The reaction mixture was allowed to warm to 0°C and stirred at this temperature for 1 hour. The reaction was quenched with a few drops of water. The reaction mixture was partitioned between diethyl ether and dilute aqueous hydrochloric acid. The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (1:1, by volume) to afford the title compound (39mg) as a white solid, m.p. 56-59°C.

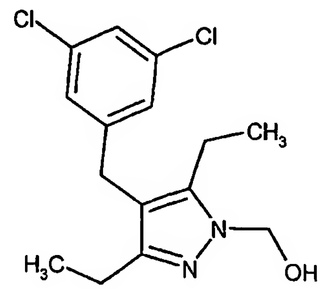
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.16 (t, 3H), 2.02 (m, 2H), 2.47 (q, 2H), 2.53 (q, 2H), 3.69 (m, 4H), 4.06 (brs, 1H), 4.20 (t, 2H), 6.97 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH^+] 341.

Microanalysis: Found: C, 59.86; H, 6.54; N, 8.14. $C_{17}H_{22}Cl_2N_2O$ requires C, 59.83; H, 6.50; N, 8.21%.

EXAMPLE 41

[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]methanol



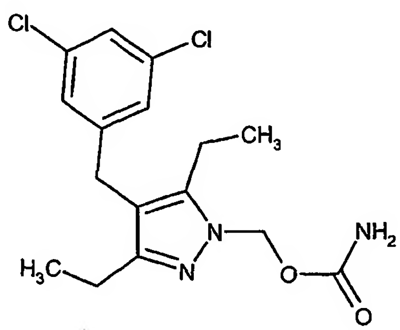
A solution of the pyrazole of Example 11 (283mg, 1.00mmol) in water (1ml) and ethanol (0.5ml) was treated with 37%$^{w}/_{w}$ aqueous formaldehyde solution (112μL, 1.50mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction was then stirred under reflux for 2 hours. The reaction mixture was diluted with water and extracted with dichloromethane. The organic extract was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (2:1, by volume) to afford the title compound (231mg) as a white solid, m.p. 117-118°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.16 (m, 6H), 2.48 (q, 2H), 2.65 (q, 2H), 3.73 (s, 2H), 5.50 (s, 2H), 5.80 (brs, 1H), 7.00 (s, 2H), 7.20 (s, 1H).

Microanalysis: Found: C, 57.48; H, 5.78; N, 8.87. $C_{15}H_{18}Cl_2N_2O$ requires C, 57.52; H, 5.79; N, 8.94%.

EXAMPLE 42

[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl carbamate



A solution of the alcohol of Example 41 (280mg, 0.90mmol) in dichloromethane (5ml) was cooled to 0°C, treated with trichloroacetyl isocyanate (128μl, 1.1mmol) and stirred at 0°C for 30 minutes. The solution was soaked into a pad of alumina (neutral, activity II, Brockmann), washed with dichloromethane and then extracted with ethyl acetate. The organic extract was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with a solvent gradient of cyclohexane:ethyl acetate (2:1, by volume) gradually changing to cyclohexane:ethyl acetate (1:1, by volume) to afford the title compound (238mg) as a solid, m.p. 153-155°C.

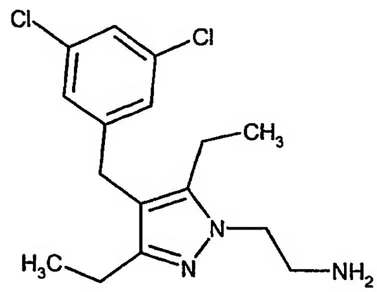
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.03 (t, 3H), 1.11 (t, 3H), 2.42 (q, 2H), 2.60 (q, 2H), 3.66 (s, 2H), 4.66 (brs, 2H), 5.94 (s, 2H), 6.92 (s, 2H), 7.13 (s, 1H).

LRMS (thermospray): m/z [MH^+] 356.

Microanalysis: Found: C, 54.04; H, 5.39; N, 11.65. $C_{16}H_{19}Cl_2N_3O_2$ requires C, 53.94; H, 5.38; N, 11.79%.

EXAMPLE 43

2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanamine



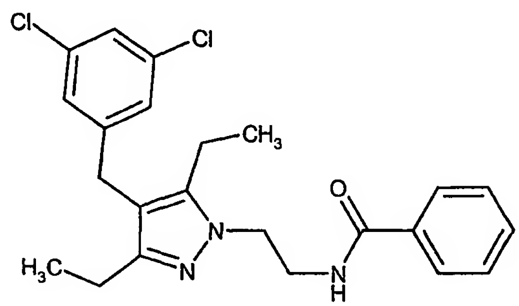
The pyrazole of Example 11 (5.47g, 19.3mmol) was mixed with 2-chloroethylamine hydrochloride (2.46g, 21.3mmol) and heated neat at 150°C for 20 hours. After cooling, the solid was partitioned between dichloromethane and 10% aqueous potassium carbonate solution. The organic extract was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol:ammonia (95:5:0, by volume) gradually changing to dichloromethane:methanol:ammonia (90:10:1, by volume) to afford the title compound (3.37g) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.03 (t, 3H), 1.15 (t, 3H), 2.45 (q, 2H), 2.52 (q, 2H), 3.16 (t, 2H), 3.71 (s, 2H), 4.06 (t, 2H), 6.97 (s, 2H), 7.18 (s, 1H).

LRMS (thermospray): m/z [MH^+] 326

EXAMPLE 44

N-{2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}benzamide



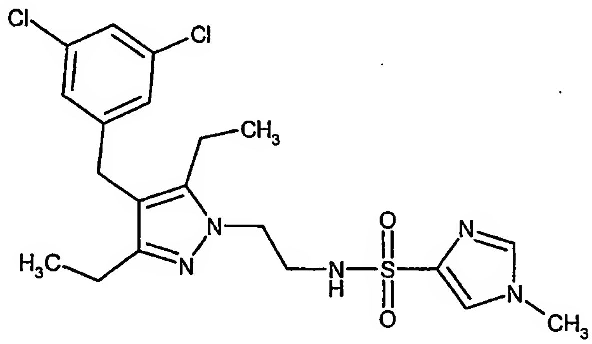
A solution of the amine of Example 43 (98mg, 0.30mmol) in dimethylformamide (3.75ml) was treated with benzoic acid (41mg, 0.33mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (64mg, 0.33mmol) and 4-dimethylaminopyridine (81mg, 0.66mmol) and stirred at room temperature for 18 hours. The solution was concentrated under reduced pressure. The residue was partitioned between dichloromethane and saturated sodium hydrogencarbonate solution. The organic extract was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) to afford the title compound (48mg) as a white solid, m.p. 115-117°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.03 (t, 3H), 1.20 (t, 3H), 2.48 (q, 2H), 2.55 (q, 2H), 3.68 (s, 2H), 3.89 (m, 2H), 4.23 (t, 2H), 6.97 (s, 2H), 7.18 (s, 1H), 7.42 (m, 2H), 7.48 (m, 1H), 7.60 (brs, 1H), 7.80 (d, 2H).

LRMS (thermospray): m/z [MH^+] 430.

EXAMPLE 45

N-{2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-1-methyl-1*H*-imidazole-4-sulfonamide



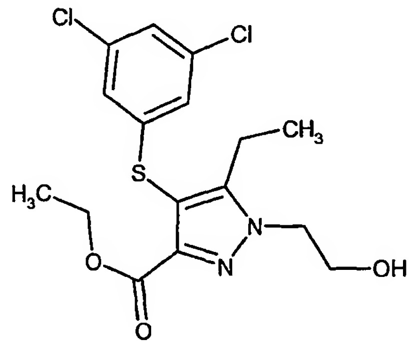
A solution of the amine of Example 43 (98mg, 0.30mmol) in dimethylformamide (3.75ml) was treated with 1-methylimidazole-4-sulphonyl chloride (60mg, 0.33mmol) and triethylamine (46µL, 0.33mmol) and the resulting mixture was stirred at room temperature for 18 hours. The solution was concentrated under reduced pressure. The residue was partitioned between dichloromethane and saturated aqueous sodium hydrogencarbonate solution. The organic extract was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) to afford the title compound (55mg) as a white solid, m.p. 172-174°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.08 (t, 3H), 2.40 (q, 2H), 2.50 (q, 2H), 3.52 (m, 2H), 3.66 (s, 2H), 3.71 (s, 3H), 4.15 (m, 2H), 6.06 (t, 1H), 6.95 (s, 2H), 7.16 (s, 1H).

LRMS (electrospray): m/z [MH^+] 470.

EXAMPLES 46 AND 47

Ethyl 4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazole-3-carboxylate (Example 46)



To a stirred suspension of the β-diketone of Preparation 36 (664mg, 1.90mmol) in ethanol (1.3ml) was added 2-hydroxyethyl hydrazine (145mg, 1.90mmol) and the resulting mixture was heated at 80°C in a sealed Reacti-vial (Trade Mark) for 3 hours. After cooling, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (3:1, by volume) and then pentane:ethyl acetate (1:1, by volume) to afford two compounds.

The more polar material was Example 46 (587mg) isolated as a pale yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.13 (t, 3H), 1.25 (t, 3H), 2.82 (q, 2H), 4.12 (q, 2H), 4.35 (m, 4H), 6.89 (s, 2H), 7.00 (s, 1H).
LRMS (electrospray): m/z [MNa^+] 411.

The less polar material was ethyl 4-[(3,5-dichlorophenyl)sulfanyl]-3-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazole-5-carboxylate (Example 47) (40mg) isolated as a colourless oil.

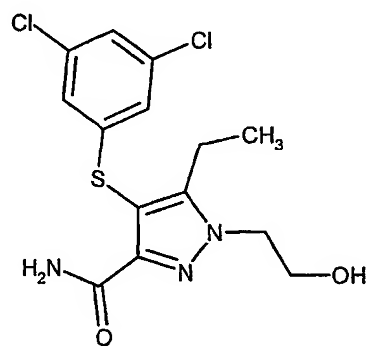
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (m, 6H), 2.61 (q, 2H), 4.03 (m, 2H), 4.04 (q, 2H), 4.64 (t, 2H), 6.83 (s, 2H), 7.03 (s, 1H).

LRMS (electrospray): m/z [MH^+] 389.

Accurate Mass: Found 389.0481 [MH^+]; $C_{16}H_{18}Cl_2N_2O_3S$ requires 389.0488 [MH^+].

EXAMPLE 48

4-[(3,5-Dichlorophenyl)sulfanyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazole-3-carboxamide



A mixture of Example 46 (407mg, 1.05mmol) and 0.880 ammonia solution was heated at 90°C in a sealed Reacti-vial (Trade Mark) for 18 hours. The precipitate was filtered off and washed with water (5ml) to afford the title compound (273mg) as a white solid, m.p. 214-216°C.

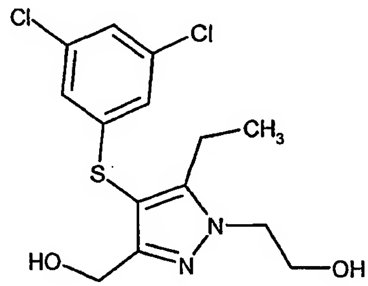
^{1}H-NMR (300MHz, CD_3OD): δ = 1.13 (t, 3H), 2.82 (q, 2H), 4.01 (t, 2H), 4.32 (t, 2H), 6.99 (s, 2H), 7.19 (s, 1H).

LRMS (thermospray): m/z [MNa^+] 382.

Microanalysis: Found: C, 46.59; H, 4.10; N, 11.23. $C_{14}H_{15}Cl_2N_3O_2S$ requires C, 46.68; H, 4.20; N, 11.66%.

EXAMPLE 49

2-[4-[(3,5-Dichlorophenyl)sulfanyl]-5-ethyl-3-(hydroxymethyl)-1*H*-pyrazol-1-yl]ethanol



A solution of Example 46 (65mg, 0.17mmol) in tetrahydrofuran (2.5ml) was cooled to -78°C and treated with lithiumaluminium hydride (1M in THF) (170μL, 0.17mmol). After stirring at -78°C for 2 hours the reaction mixture was allowed to warm to 0°C for 1 hour and was then allowed to warm to room temperature. After stirring at this temperature for 18 hours, water (1ml) was added. The reaction mixture was partitioned between ethyl acetate (25ml) and water (25ml). The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume) to afford the title compound (42mg) as a colourless oil, which solidified on standing, m.p. 89-90°C.

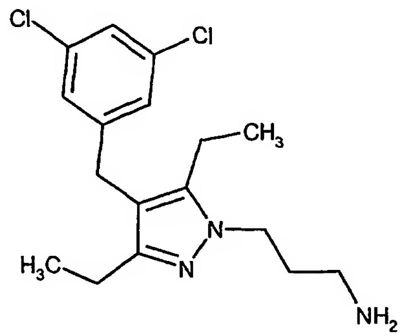
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.06 (t, 3H), 2.09 (brs, 1H), 2.67 (q, 2H), 3.13 (brs, 1H), 4.03 (m, 2H), 4.18 (t, 2H), 4.60 (m, 2H), 6.92 (s, 2H), 7.03 (s, 1H).

LRMS (electrospray): m/z [MNa^+] 369.

Accurate Mass: Found 347.0383 [MH^+]; $C_{14}H_{16}Cl_2N_2O_2S$ requires 347.0383 [MH^+].

EXAMPLE 50

3-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]-1-propanamine



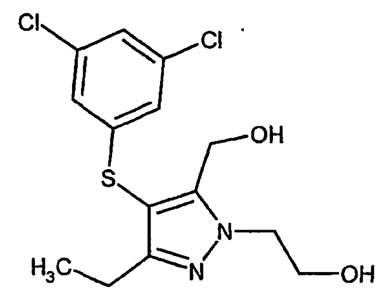
The pyrazole of Example 11 (200mg, 0.71mmol) was mixed with 3-chloropropylamine hydrochloride (138mg, 1.06mmol). The resulting mixture was heated neat at 150°C, for 24 hours, under a nitrogen atmosphere. After cooling, the reaction mixture was partitioned between dichloromethane (30ml) and saturated aqueous sodium hydrogencarbonate solution (30ml). The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol:ammonia (90:10:0, by volume) gradually changing to dichloromethane:methanol:ammonia (90:10:1, by volume) to afford the title compound (203mg) as a brown oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.04 (t, 3H), 1.13 (t, 3H), 1.96 (m, 2H), 2.45 (q, 2H), 2.50 (q, 2H), 2.78 (t, 2H), 3.69 (s, 2H), 4.09 (t, 2H), 6.99 (s, 2H), 7.19 (s, 1H).

LRMS (electrospray): m/z [MH^+] 342.

EXAMPLE 51

2-[4-[(3,5-Dichlorophenyl)sulfanyl]-3-ethyl-5-(hydroxymethyl)-1*H*-pyrazol-1-yl]ethanol



The title compound was prepared by a similar method to that of Example 49 using Example 47 except that the crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (1:1, by volume) to afford the title compound as a white solid, m.p. 106-108°C.

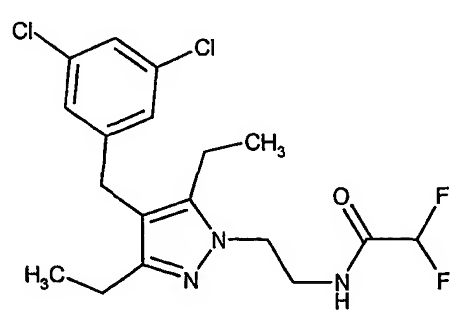
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.20 (t, 3H), 2.61 (q, 2H), 2.78 (brs, 1H), 2.97 (brs, 1H), 4.09 (m, 2H), 4.39 (t, 2H), 4.69 (m, 2H), 6.84 (s, 2H), 7.08 (s, 1H).

LRMS (electrospray): m/z [MNa^+] 369.

Accurate Mass: Found 347.0394 [MH^+]; $C_{14}H_{16}Cl_2N_2O_2S$ requires 347.0383 [MH^+].

EXAMPLE 52

N-{2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2,2-difluoroacetamide



Standard solution: The amine of Example 43 (372mg, 1.14mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (437mg, 2.28mmol) and 4-dimethylaminopyridine (342mg, 2.28mmol) were dissolved in dimethylformamide (14.25ml).

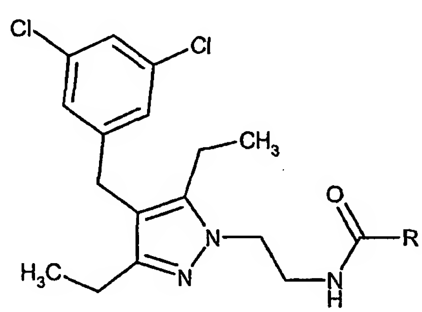
Difluoroacetic acid (2.5μl, 40μmol) was treated with the standard solution of amine (250μL) in a 96 well plate and the mixture was shaken for 18 hours. The reaction mixture was filtered and the filtrate was purified by HPLC (Magellen C_8(2) 150x10mm column; a gradient mobile phase was used, 5:95 (by volume)→95:5 (by volume) acetonitrile: (water, 95% by volume/trifluoroacetic acid, 0.1% by volume/acetonitrile 5%, by volume)).

Retention time: 6.05 minutes

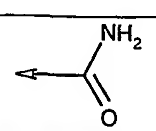
LRMS (electrospray): m/z [MH^+] 404.

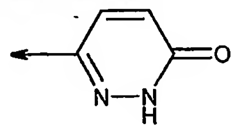
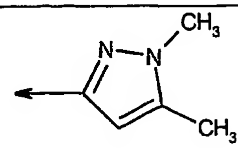
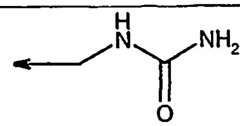
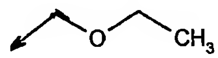
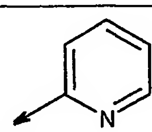
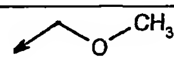
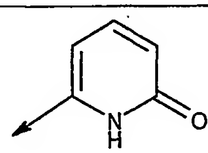
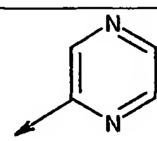
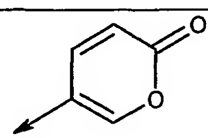
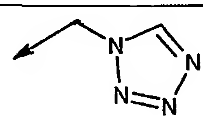
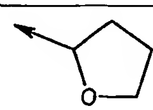
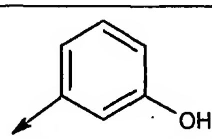
EXAMPLES 53-70

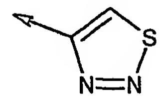
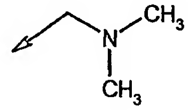
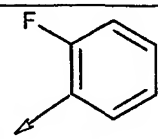
The compounds of the following tabulated Examples of the general formula:



were prepared by a similar method to that of Example 52 using the appropriate acid.

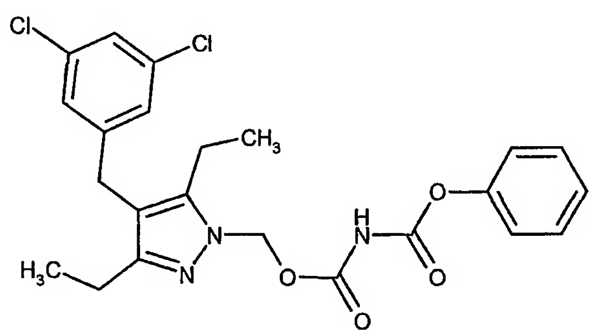
Example No.	R	HPLC retention time (minutes)	LRMS (electrospray) m/z [M^+] =
53		5.15	397

54		4.96	448
55		5.73	448
56		4.37	426
57		6.00	412
58		6.20	431
59		5.61	398
60		5.12	447
61		5.84	432
62		5.96	448
63		5.22	436
64		5.82	424
65		5.49	446

66		4.96	384
67		6.05	438
68		3.85	411
69		5.54	393
70		6.46	448

EXAMPLE 71

[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl phenyl imidodicarbonate



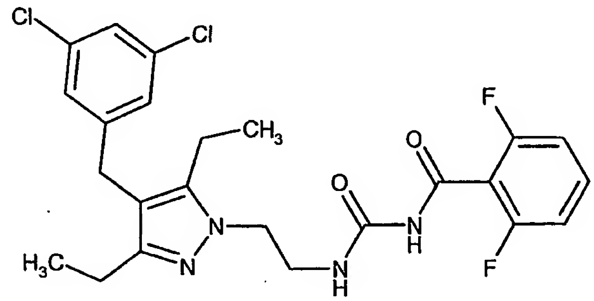
A solution of the alcohol of Example 41 (6.3mg, 20μmol) in dimethylformamide (250μL) was treated with phenyl isocyanatoformate (3.6mg, 22μmol) and the mixture was shaken for 1.5 hours. The reaction mixture was filtered and the filtrate was purified by HPLC (Hypersil Thermoquest Luna C_8 150x10mm column; a gradient mobile phase was used, 10:90 (by volume)→95:5 (by volume) acetonitrile:(water, 95% by volume/trifluoroacetic acid, 0.1% by volume/acetonitrile 5%, by volume)).

Retention time: 7.64 minutes

LRMS (electrospray): m/z [MH^+] 476.

EXAMPLE 72

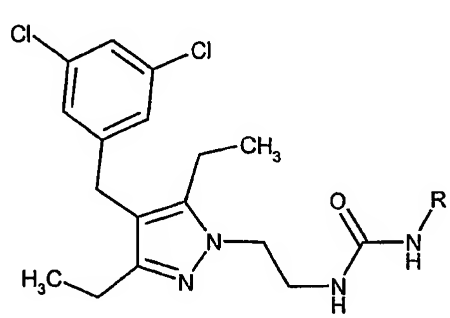
N-{2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-*N'*-(2,6-difluorobenzoyl)urea



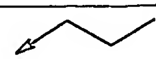
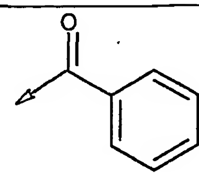
A solution of the amine of Example 43 (6.5mg, 20μmol) in dimethylformamide (250μL) was treated with 2,6-difluorobenzoylisocyanate (4.0mg, 22μmol) and the mixture was shaken for 18 hours. The reaction mixture was filtered and the filtrate was purified by HPLC (Hypersil Thermoquest Luna C_8 150x10mm column; a gradient mobile phase was used, 10:90 (by volume)→95:5 (by volume) acetonitrile:(water, 95% by volume/trifluoroacetic acid, 0.1% by volume/acetonitrile 5%, by volume)).
Retention time: 6.8-7.4 minutes
LRMS (electrospray): m/z [MH^+] 509.

EXAMPLES 73-74

The compounds of the following tabulated Examples of the general formula:

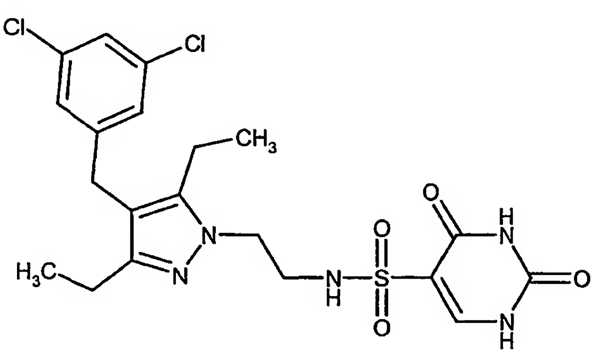


were prepared by a similar method to that of Example 72 using the appropriate isocyanate.

Example No.	R	HPLC retention time (minutes)	LRMS (electrospray) m/z [M⁺] =
73		6.23	411
74		7.21	473

EXAMPLE 75

N-{2-[4-(3,5-Dichlorobenzyl)-3,5-diethyl-1H-pyrazol-1-yl]ethyl}-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonamide

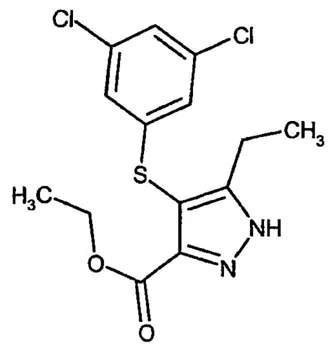


A solution of the amine of Example 43 (6.5mg, 20μmol) and triethylamine (6μl, 40μmol) in dimethylformamide (250μL) was treated with 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonyl chloride (J. Am. Chem. Soc., 1956, *78*, 401) (0.8mg, 4.0μmol) and the mixture was shaken for 18 hours. The reaction mixture was filtered and the filtrate was purified by HPLC (Hypersil Thermoquest Luna C_8 150x10mm column; a gradient mobile phase was used, 10:90 (by volume)→95:5 (by volume) acetonitrile:(water, 95% by volume/trifluoroacetic acid, 0.1% by volume/acetonitrile 5%, by volume)).

Retention time: 6.00 minutes
LRMS (electrospray): m/z [MH^+] 500.

EXAMPLE 76

Ethyl 4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1*H*-pyrazole-3-carboxylate

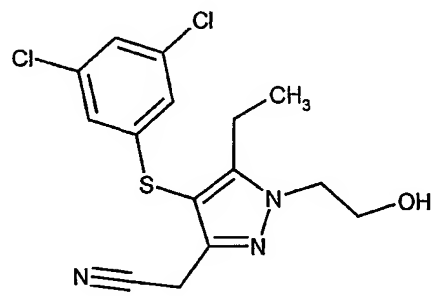


To a stirred solution of the β-diketone of Preparation 36 (2.00g, 5.73mmol) in ethanol (3ml) was added hydrazine monohydrate (278μl, 5.73mmol) and the resulting mixture was heated at 80°C in a sealed Reacti-vial (Trade Mark) for 2 hours. After cooling, the mixture was dissolved in water and the resulting solution was extracted with dichloromethane and followed by ethyl acetate. The combined organic phases were washed with brine and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (5:1, by volume) and then cyclohexane:ethyl acetate (3:1, by volume) to afford the product as an oily white solid. This material was washed with pentane and the white solid was collected by filtration and air dried to give a pure sample of the title compound (450mg), m.p. 138-139°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.21 (m, 6H), 2.72 (q, 2H), 4.32 (q, 2H), 6.84 (s, 2H), 7.04 (s, 1H).
LRMS (electrospray): m/z [$M-H^+$] 343.
Microanalysis: Found: C, 48.53; H, 3.95; N, 8.00. $C_{14}H_{14}Cl_2N_2O_2S$ requires C, 48.71; H, 4.09; N, 8.11%.

EXAMPLE 77

[4-[(3,5-Dichlorophenyl)sulfanyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-3-yl]acetonitrile



A solution of the protected alcohol of Preparation 39 (70mg, 0.15mmol) in tetrahydrofuran (1ml) was treated with tetrabutylammonium fluoride (1M in THF) (300µL, 0.30mmol), at room temperature. After the reaction mixture had stirred for 3 hours the solution was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (3:1, by volume) to afford the title compound (30mg) as a white solid, m.p. 84-85°C.

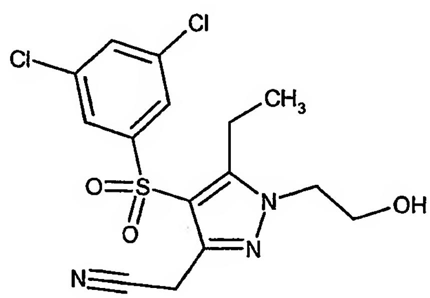
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (m, 3H), 2.75 (q, 2H), 2.83 (t, 1H), 3.63 (s, 2H), 4.12 (m, 2H), 4.22 (m, 2H), 6.82 (s, 2H), 7.10 (s, 1H).

LRMS (electrospray): m/z [M-H$^+$] 354.

Microanalysis: Found: C, 50.86; H, 4.28; N, 11.70. $C_{15}H_{15}Cl_2N_3OS$ requires C, 50.57; H, 4.24; N, 11.79%.

EXAMPLE 78

[4-[(3,5-Dichlorophenyl)sulfonyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-3-yl]acetonitrile



To a stirred solution of the pyrazole (68mg, 0.14mmol) of Preparation 39 in methanol (2ml) was added dichloromethane (3ml), followed by meta-chloroperoxybenzoic acid (60% $^{w}/_{w}$) (125mg, 0.43mmol). After 18 hours the mixture was partitioned between dichloromethane and water. The aqueous component was separated and further extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give a white solid. To a stirred solution of this material in THF (2ml) was added water (2ml) followed by acetic acid (2ml). After 18 hours at room temperature the mixture was partitioned between water and dichloromethane and the aqueous component was separated and further extracted with dichloromethane. The combined organic phases were washed with aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (2:1, by volume) followed by cyclohexane:ethyl actetate (1:1, by volume) to afford the title compound (45mg) as a white solid, m.p. 117-118^{o}C.

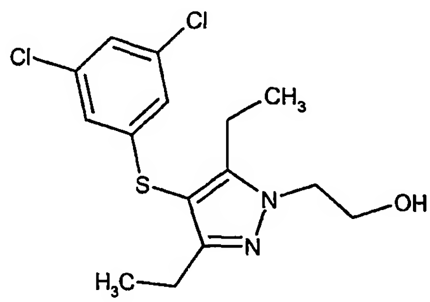
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.11 (t, 3H), 2.41 (t, 1H), 2.89 (q, 2H), 4.02 (s, 2H), 4.05 (m, 4H), 7.57 (s, 2H), 7.79 (s, 1H).

LRMS (electrospray): m/z [MH^+] 388.

Microanalysis: Found: C, 46.39; H, 3.89; N, 10.53. $C_{15}H_{15}Cl_2N_3O_3S$ requires C, 46.40; H, 3.89; N, 10.82%.

EXAMPLE 79

2-{4-[(3,5-Dichlorophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol



To a stirred solution of the diketone (500mg, 1.64mmol) of Preparation 41 in ethanol (1ml) was added 2-hydroxyethylhydrazine (113μl, 1.80mmol). The reaction mixture was heated at 80°C in a sealed Reacti-vial (Trade Mark) for 4 hours. After cooling, the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (3:1, by volume) to afford the title compound as a yellow solid (349mg), 77-79°C.

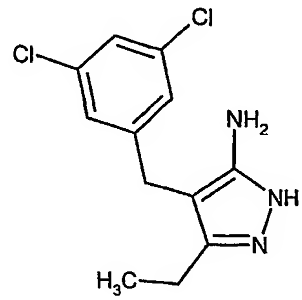
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.04 (t, 3H), 1.18 (t, 3H), 2.52 (q, 2H), 2.62 (q, 2H), 3.64 (s, 1H), 4.03 (m, 2H), 4.17 (m, 2H), 6.79 (s, 2H), 7.02 (s, 1H).

LRMS (electrospray): m/z [MH^+] 345.

Microanalysis: Found: C, 51.88; H, 5.20; N, 8.03. $C_{15}H_{18}Cl_2N_2OS$ requires C, 52.18; H, 5.25; N, 8.11%.

EXAMPLE 80

4-(3,5-Dichlorobenzyl)-3-ethyl-1*H*-pyrazol-5-amine



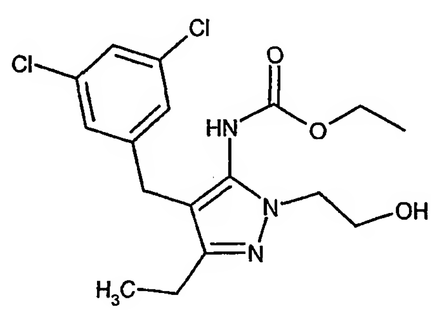
To a stirred solution of the nitrile (500mg, 1.95mmol) of Preparation 43 in ethanol (50ml) was added hydrazine monohydrate (100mg, 1.95mmol) and the mixture was heated under reflux. After 15 hours the reaction mixture was cooled and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5, by volume) to afford the title compound as a yellow oil (250mg).

^{1}H-NMR (400MHz, CD_3OD): δ = 1.05 (t, 3H), 2.43 (q, 2H), 3.66 (s, 2H), 7.09 (s, 2H), 7.19 (s, 1H).

LRMS (thermospray): m/z [MH^+] 345.

EXAMPLE 81

Ethyl 4-(3,5-dichlorobenzyl)-3-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-5-ylcarbamate



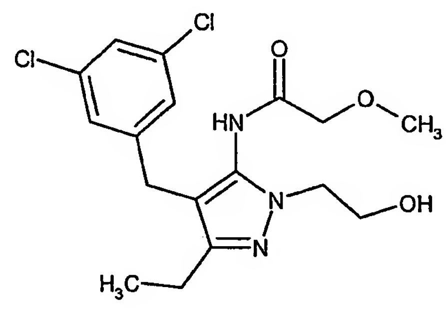
To a stirred solution of the pyrazole (150mg, 0.35mmol) of Preparation 44 and triethylamine (70µl, 0.53mmol) in dichloromethane (6ml) was added ethyl chloroformate (40µl, 0.39mmol) and the mixture was heated under reflux. After 15 hours the solution was concentrated under reduced pressure. To a solution of the residue in pyridine (2ml) was added ethyl chloroformate (40µl, 0.39mmol). After 7 days at room temperature the solvent was removed under reduced pressure and the residue was filtered through silica, eluting with dichloromethane:methanol:ammonia (98:2:0.2, by volume). The resulting solution was concentrated under reduced pressure and the residue was dissolved in a mixture of tetrahydrofuran (2ml), acetic acid (2ml) and water (1ml). After stirring at room temperature for 15 hours the reaction mixture was partitioned between water and dichloromethane. The aqueous phase was separated and further extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane followed by dichloromethane:methanol:ammonia (95:5:0.5, by volume) to afford the title compound (18mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.20 (m, 6H), 2.49 (m, 2H), 3.71 (s, 2H), 3.99 (m, 2H), 4.10 (m, 4H), 6.30 (m, 1H), 7.03 (s, 2H), 7.20 (s, 1H).

LRMS (electrospray): m/z [M-H$^+$] 384.

EXAMPLE 82

N-[4-(3,5-Dichlorobenzyl)-3-ethyl-1-(2-hydroxyethyl)-1H-pyrazol-5-yl]-2-methoxyacetamide



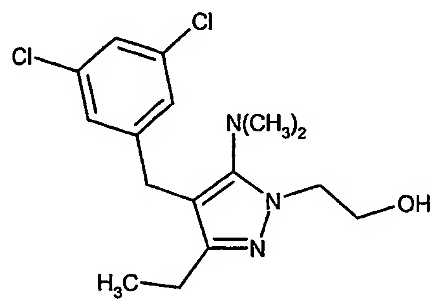
To a stirred mixture of the pyrazole (200mg, 0.47mmol) of Preparation 44 and methoxyacetyl chloride (56mg, 0.52mmol) in dichloromethane (10ml) was added triethylamine (72µl, 0.52mmol). After 15 hours at room temperature the solvent was removed under reduced pressure and the resulting orange oil was partitioned between dichloromethane and water. The organic phase was separated, washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. To a stirred solution of the residue in acetic acid (2ml) was added water (1ml). After 3 days at room temperature the mixture was heated at 60°C. After 4 hours the solution was cooled to room temperature and partitioned between aqueous sodium carbonate solution and dichloromethane. The organic phase was separated and twice washed with water, twice washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The title compound was isolated as a white solid (100mg) which was used without further purification, m.p. 142-144°C.

^{1}H-NMR (400MHz, CF_3CO_2D): δ = 1.38 (t, 3H), 2.90 (q, 2H), 3.52 (s, 3H), 3.88 (s, 2H), 4.16 (s, 2H), 4.21 (m, 2H), 4.58 (m, 2H), 7.03 (s, 2H), 7.30 (s, 1H).

LRMS (thermospray): m/z [MH$^+$] 386.

EXAMPLE 83

2-[4-(3,5-Dichlorobenzyl)-5-(dimethylamino)-3-ethyl-1*H*-pyrazol-1-yl]ethanol



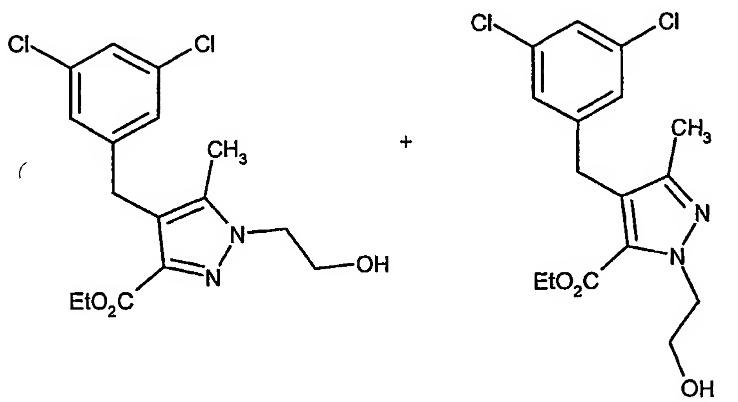
A stirred solution of the pyrazole (300mg, 0.70mmol) of Preparation 44 and paraformaldehyde (46mg, 1.54mmol) in formic acid (2ml) was heated under reflux. After 15 hours the mixture was cooled and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane followed by dichloromethane:methanol (99:1, by volume) to afford the title compound (50mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.09 (t, 3H), 2.38 (q, 2H), 2.62 (s, 6H), 3.77 (s, 2H), 3.91 (m, 2H), 4.04 (m, 2H), 4.23 (t, 1H), 6.95 (s, 2H), 7.17 (s, 1H).

LRMS (thermospray): m/z [MH^+] 342.

EXAMPLES 84 AND 85

Ethyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carboxylate (Examples 84) and ethyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazole-5-carboxylate (Example 85)



The title compounds were prepared by a similar method to that of Examples 27 and 28 using the β-diketone of Preparation 22. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (1:1, by volume) to afford the two isomers.

Less polar isomer (Example 85):

Shown to be ethyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazole-5-carboxylate by nOe experiments. Isolated as a white solid, m.p. 105.8-107.5°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.35 (t, 3H), 2.20 (s, 3H), 3.10 (t, 1H), 4.00 (s, 2H), 4.01 (m, 2H), 4.30 (q, 2H), 4.67 (m, 2H), 6.98 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH^+] 357.

Microanalysis: Found: C, 53.81; H, 5.02; N, 7.59. $C_{16}H_{18}N_2O_3$ requires C, 53.80; H, 5.08; N, 7.84%.

More polar isomer (Example 84):

Ethyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carboxylate was isolated as a white solid, 110.7-112.4°C.

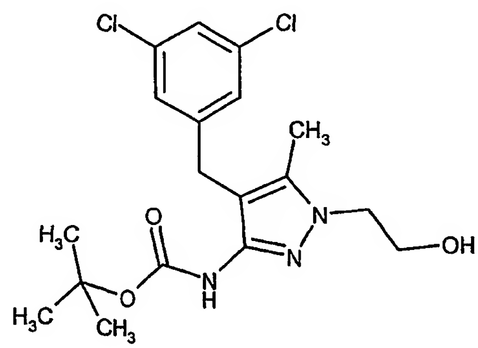
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.35 (t, 3H), 2.21 (s, 3H), 2.70 (brs, 1H), 4.01 (m, 4H), 4.22 (m, 2H), 4.33 (q, 2H), 7.00 (s, 2H), 7.19 (s, 1H).

LRMS (thermospray): m/z [MH^+] 357.

Microanalysis: Found: C, 53.53; H, 5.06; N, 7.59. $C_{16}H_{18}N_2O_3$ requires C, 53.80; H, 5.08; N, 7.84%.

EXAMPLE 86

tert-Butyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-3-ylcarbamate



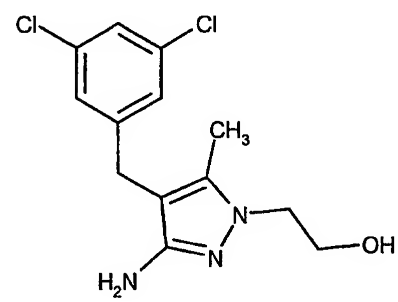
A suspension of the carboxylic acid of Preparation 23 (550mg, 1.67mmol) in *tert*-butanol (8.35ml) was treated with triethylamine (244μL, 1.84mmol) and diphenylphosphoryl azide (396μL, 1.84mmol) and the reaction mixture was stirred under reflux for 18 hours, under a nitrogen atmosphere. After cooling, the solution was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (x3). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (1:2, by volume) followed by dichloromethane:methanol:ammonia (95:5:0.5, by volume) to afford the title compound (160mg).

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.44 (s, 9H), 2.17 (s, 3H), 3.42 (s, 1H), 3.77 (s, 2H), 3.92 (m, 2H), 4.02 (m, 2H), 6.43 (s, 1H), 6.99 (s, 2H), 7.18 (s, 1H).

LRMS (thermospray): m/z [MH^+] 400.

EXAMPLE 87

2-[3-Amino-4-(3,5-dichlorobenzyl)-5-methyl-1*H*-pyrazol-1-yl]ethanol



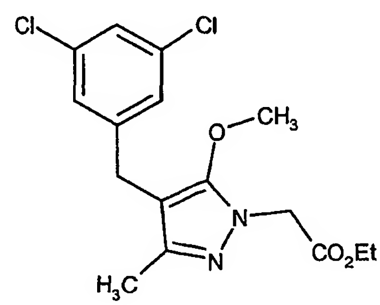
A solution of the protected amine of Example 86 (50mg, 0.13mmol) in 1,4-dioxan was treated with 4M hydrogen chloride in 1,4-dioxan (320μL, 1.25mmol) and stirred at room temperature for 2 days. The solution was concentrated under reduced pressure. The residue was diluted with water (15ml) and extracted with ethyl acetate (3x10ml). The combined organic phases were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford the title compound as a white solid and as the hydrochloride salt (19.5mg).

^{1}H-NMR (300MHz, d_6-DMSO): δ = 2.13 (s, 3H), 3.59 (m, 2H), 3.69 (s, 2H), 3.89 (m, 2H), 7.09 (s, 2H), 7.25 (s, 1H).

LRMS (thermospray): m/z [MH^+] 300.

EXAMPLE 88

Ethyl [4-(3,5-dichlorobenzyl)-5-methoxy-3-methyl-1*H*-pyrazol-1-yl]acetate



A suspension of the ester of Preparation 26 (100mg, 0.29mmol) in toluene (4ml) was treated with triphenylphosphine (115mg, 0.44mmol), followed by methanol (15μL, 0.30mmol) then diethyl azodicarboxylate (69μL, 0.44mmol) and the resulting mixture was stirred at room temperature, under a nitrogen atmosphere for 18 hours. The reaction mixture was diluted with ethyl acetate and washed with 10% aqueous sodium carbonate solution. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl actetate (3:1, by volume) to afford the title compound (73mg) as a colourless oil, which solidified under reduced pressure.

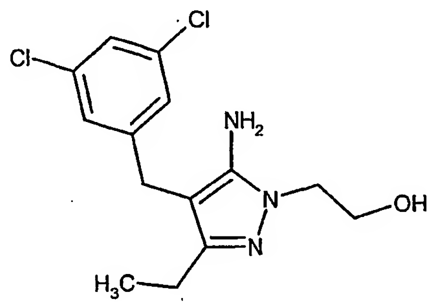
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.31 (t, 3H), 2.08 (s, 3H), 3.78 (s, 2H), 3.81 (s, 3H), 4.27 (q, 2H), 4.73 (s, 2H), 7.03 (s, 2H), 7.20 (s, 1H).

LRMS (thermospray): m/z [MH^+] 357.

Microanalysis: Found: C, 53.66 H, 5.08; N, 7.84. $C_{16}H_{18}Cl_2N_2O_3$ requires C, 53.80; H, 5.08; N, 7.84%.

EXAMPLE 89

2-[5-Amino-4-(3,5-dichlorobenzyl)-3-ethyl-1*H*-pyrazol-1-yl]ethanol

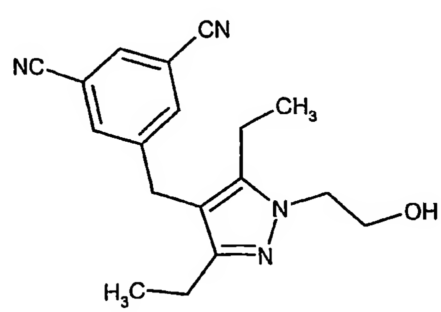


To a stirred solution of the nitrile (500mg, 1.95mmol) of Preparation 43 in ethanol (50ml) was added 2-hydroxyethylhydrazine (153mg, 1.95mmol) and the mixture was heated under reflux. After 15 hours the mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5, by volume) to afford the title compound (450mg) as a white solid, m.p. 135°C.

^{1}H-NMR (400MHz, DMSO): δ = 0.90 (t, 3H), 2.19 (q, 2H), 3.58 (m, 4H), 3.82 (t, 2H), 4.82 (t, 1H), 4.90 (s, 2H), 7.07 (s, 2H), 7.30 (s, 1H).
LRMS (thermospray): m/z [MH$^+$] 314.
Microanalysis: Found: C, 53.33; H, 5.50; N, 13.20. $C_{14}H_{17}Cl_2N_3O$ requires C, 53.52; H, 5.45; N, 13.37%.

EXAMPLE 90

5-{[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]methyl}isophthalonitrile



2-Hydroxyethylhydrazine (34mg, 0.44mmol) was added to a stirred solution of the diketone (105mg, 0.4mmol) of Preparation 45 in glacial acetic acid (3ml) at room temperature under nitrogen. After stirring for 3 days the acetic acid was evaporated under reduced pressure and the residue was partitioned between 10% aqueous potassium carbonate solution (40ml) and dichloromethane (40ml). The organic phase was separated, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to give the title compound as a white solid (76mg) m.p. 115-117°C.

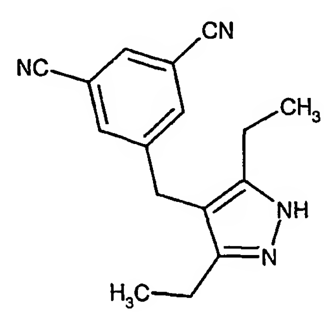
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.0 (3H, t), 1.1 (3H, t), 1.55 (1H, br.s), 2.37 (2H, q), 2.48 (2H, q), 3.79 (2H, s), 4.02 (2H, m), 4.08 (2H, m), 7.55 (2H, s), 7.71 (1H, s).

LRMS (thermospray): m/z [MH^+] 309.

Microanalysis: Found: C, 69.64; H, 6.54; N, 18.06. $C_{16}H_{16}N_2O_2$ requires C, 70.11; H, 6.54; N, 18.17%.

EXAMPLE 91

5-[(3,5-Diethyl-1*H*-pyrazol-4-yl)methyl]isophthalonitrile



Hydrazine hydrate (49μL, 1mmol) was added to a stirred solution of the diketone (237mg, 0.9mmol) of Preparation 45 in glacial acetic acid (3ml) at room

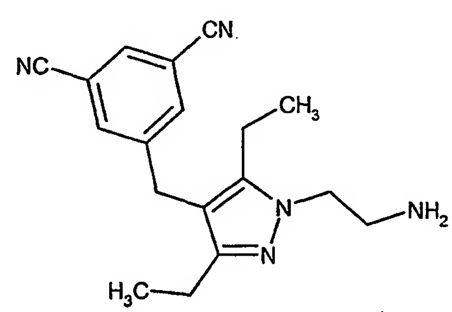
temperature under nitrogen. After stirring for 3 days the acetic acid was evaporated under reduced pressure and the residue was partitioned between 10% aqueous potassium carbonate solution (40ml) and dichloromethane (40ml). The organic phase was separated, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2, by volume) to give the title compound as a white solid (188mg) m.p. 141-143°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (6H, t), 2.47 (4H, q), 3.82 (2H, s), 7.58 (2H, s), 7.73 (1H, s).

LRMS (thermospray): m/z [MH^+] 265.

EXAMPLE 92

5-{[1-(2-Aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]methyl}isophthalonitrile



A stirred mixture of the pyrazole (106mg, 0.4mmol) of Example 91 and 2-chloroethylamine hydrochloride (70mg, 0.6mmol) was heated at 150°C under nitrogen for 18 hours. After cooling the mixture was partitioned between 10% aqueous potassium carbonate (40ml) and dichloromethane (40ml) and the organic layer was dried over magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:methanol (98:2, by

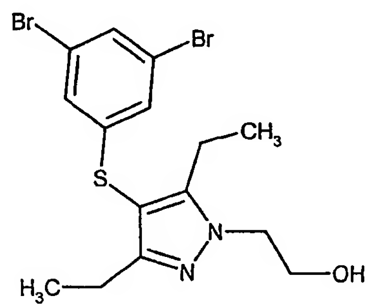
volume) and then dichloromethane:methanol:0.880 ammonia (95:5:0.5, by volume) to give the title compound as a white solid (51mg) m.p. 100-105^{o}C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.02 (3H, t), 1.09 (3H, t), 1.49 (2H, br.s), 2.38 (2H, q), 2.52 (2H, q), 3.13 (2H, t), 3.78 (2H, s), 4.04 (2H, t), 7.58 (2H, s), 7.74 (1H, s).

LRMS (electrospray): m/z [MH^{+}] 308.

EXAMPLE 93

2-{4-[(3,5-Dibromophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol

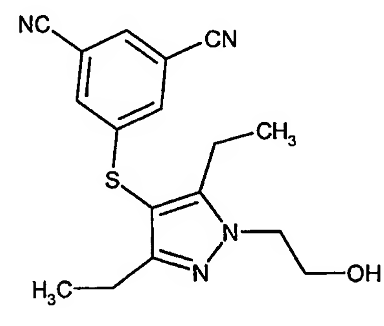


2-Hydroxyethylhydrazine (0.43mL, 6.3mmol) was added to a suspension of the diketone (2.5g, 6.3mmol) from Preparation 49 in glacial acetic acid (2ml) and the mixture was stirred for three days. 2-Hydroxyethylhydrazine (0.5mL, 7.3mmol) was added and the mixture was stirred for 16 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate (100ml) and water (150ml). The aqueous layer was extracted with ethyl acetate (100ml) and the combined organic layers were washed with brine (100ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane gradually changing to dichloromethane:ethyl acetate (17:3, by volume) to provide the title compound (1.3g) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.11 (t, 3H), 1.20 (t, 3H), 2.6 (q, 2H), 2.7 (q, 2H), 4.10 (m, 2H), 4.18 (m, 2H), 7.02 (s, 2H), 7.37 (s, 1H).
LRMS (thermospray): m/z [MH^+] 435.
Microanalysis: Found: C, 41.29; H, 4.17; N, 6.36. $C_{15}H_{18}Br_2N_2OS$ requires C, 41.49; H, 4.18; N, 6.45%.

EXAMPLE 94

5-{[3,5-Diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]sulfanyl}isophthalonitrile



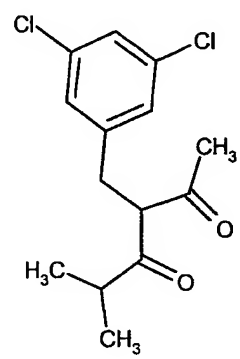
5-{[1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]sulfanyl}isophthalonitrile (180mg, 0.4mmol) (Preparation 51) was treated with tetrabutylammonium fluoride (1M solution in tetrahydrofuran, 0.8ml, 0.8mmol) and the resulting solution was stirred for $2^1/_2$ hours. The mixture was concentrated under reduced pressure to give a brown oil. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate:dichloromethane (1:4, by volume) to provide the title compound (70mg) as a yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.11 (t, 3H), 1.19 (t, 3H), 2.56 (q, 2H), 2.69 (q, 2H), 3.50 (br.s, 1H), 4.12 (m, 2H), 4.22 (m, 2H), 7.41 (s, 2H), 7.61 (s, 1H).
LRMS (electrospray): m/z [MH^+] 327.

The following Preparations describe the preparation of certain intermediates used in the preceding Examples.

PREPARATION 1

3-(3,5-Dichlorobenzyl)-5-methyl-2,4-hexanedione



Method A:

5% Palladium on barium sulphate (10mg) was added to a stirred solution of the more polar alkene isomer of Preparation 8 (100mg) in ethanol (2.5ml) and the resulting mixture was stirred under an atmosphere of hydrogen (103.4kPa, 15 psi) for 3 hours. The mixture was filtered through a filter aid (Arbocel (Trade Mark))(caution - fire hazard) and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (10:1, by volume) to give the title compound (72mg) as a 43:57 mixture with its enol tautomer as estimated by ^{1}H-NMR and as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.03 (d, 6H, diketone and enol), 2.02 (s, 3H, enol), 2.11 (s, 3H, diketone), 2.52 (heptet, 1H, diketone), 2.61 (heptet, 1H, d, enol), 3.00 (dd, 1H, diketone), 3.06 (dd, 1H, diketone), 3.60 (s, 2H, enol), 4.00 (t, 1H, diketone), 6.98 and 7.00 (2s, 2x2H, diketone and enol), 7.18 (s, 1H, diketone and enol).

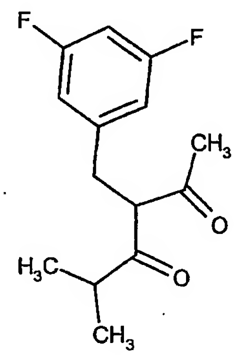
LRMS (thermospray): m/z [MH^+] 304.

Method B:

The less polar alkene isomer of Preparation 8 was reduced in the same way as for the more polar isomer in Method A above but stirring the mixture for 9 hours and flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (20:1, by volume) then pentane:ether (10:1, by volume) to give the title compound as a yellow oil.

PREPARATION 2

3-(3,5-Difluorobenzyl)-5-methyl-2,4-hexanedione



Method A:

5% Palladium on barium sulphate (56mg) was added to a stirred solution of the more polar alkene isomer of Preparation 11 (560mg) in ethanol (16ml) and the resulting mixture was stirred under an atmosphere of hydrogen (103.4kPa, 15 psi) for 4 hours. The mixture was filtered through a filter aid (Arbocel (Trade Mark))(caution - fire hazard) and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:ether (10:1, by volume) to give the title compound (513.1mg) as a 35:65 mixture with its enol tautomer as estimated by ^{1}H-NMR as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.03 (d, 6H, diketone and enol), 2.03 (s, 3H, enol), 2.13 (s, 3H, diketone), 2.55 (heptet, 1H, diketone), 2.65 (heptet, 1H, enol), 3.03 (dd, 1H, diketone), 3.11 (dd, 1H, diketone), 3.65 (s, 2H, enol), 4.03 (t, 1H, diketone), 6.65 (m, 3H, diketone and enol).

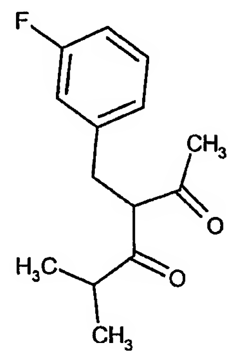
LRMS (electrospray): m/z [MNa^+] 277.

Method B:

The less polar alkene isomer of Preparation 11 was reduced in the same way as for the more polar isomer in Method A above but stirring the mixture for 25 hours to give the title compound as a yellow oil.

PREPARATION 3

3-(3-Fluorobenzyl)-5-methyl-2,4-hexanedione

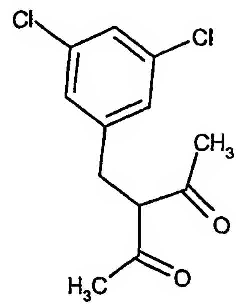


The title compound was prepared by a method similar to that of Preparation 2 using the alkene isomers of Preparation 12 to give the title compound as a 38:62 mixture with its enol tautomer as estimated by ^{1}H-NMR as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.06 (d, 6H, diketone and enol), 2.06 (s, 3H, enol), 2.16 (s, 3H, diketone), 2.55 (heptet, 1H, diketone), 2.73 (heptet, 1H, enol), 3.08 (dd, 1H, diketone), 3.16 (dd, 1H, diketone), 3.68 (s, 2H, enol), 4.10 (t, 1H, diketone), 6.89 (m, 3H, diketone and enol), 7.27 (m, 1H, diketone and enol).
LRMS (electrospray): m/z [MNa^+] 259.

PREPARATION 4

3-(3,5-Dichlorobenzyl)-2,4-pentanedione

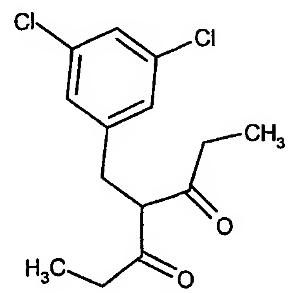


To a solution of the alkene of Preparation 9 (6.4g, 24.9mmol) in ethanol (100ml) and ethyl acetate (40ml) was added 5% palladium on barium sulphate (640mg) and the resulting mixture was stirred under an atmosphere of hydrogen (103.4kPa, 15 psi) for 18 hours. The mixture was filtered through a filter aid (Arbocel (Trade Mark))(caution - fire hazard) under nitrogen and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (10:1, by volume) and then pentane:ethyl acetate (7:1, by volume) to give the title compound (5.3g) as a mixture with its enol tautomer as shown by ^{1}H-NMR as a yellow powder, m.p. 85-87°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.02 (s, 6H, enol), 2.15 (s, 6H, diketone), 3.06 (d, 2H, diketone), 3.60 (s, 2H, enol), 3.93 (t, 1H, diketone), 7.00 (s, 2H, enol), 7.03 (s, 2H, diketone), 7.21 (s, 1H, diketone and enol), 16.78 (s, 1H, enol).
LRMS (electrospray): m/z [M-H$^+$] 257.
Microanalysis: Found: C, 55.91; H, 4.72. $C_{12}H_{12}Cl_2O_2$ requires C, 55.62; H, 4.67.

PREPARATION 5

4-(3,5-Dichlorobenzyl)-3,5-heptanedione

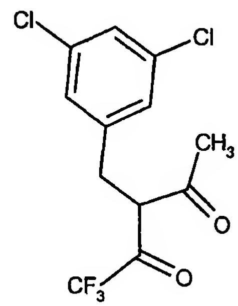


The title compound was prepared by a method similar to that of Preparation 1, Method B using the alkene of Preparation 14 and purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl acetate (20:1, by volume) and then pentane:ethyl acetate (10:1, by volume) to give the title compound as a mixture with its enol tautomer as estimated by ^{1}H-NMR and as an orange oil. A small amount (*ca.*10%) of dechlorinated impurities presumably arising from over reduction were detected by ^{1}H-NMR. This over reduction could probably be avoided by using the alternative reduction procedure of Preparation 6.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.00 (m, 6H, diketone and enol), 2.40 (m, 4H, diketone and enol), 3.11 (d, 2H, diketone), 3.64 (d, 2H, enol), 3.97 (t, 1H, diketone), 7.03 (d, 2H), 7.22 (s, 1H), 17.02 (s, 1H, enol).

PREPARATION 6

3-(3,5-Dichlorobenzyl)-1,1,1-trifluoro-2,4-pentanedione

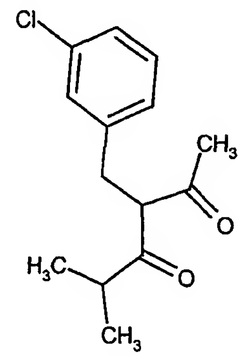


To a solution of a mixture of the alkenes of Preparation 13 (100mg, 0.321mmol) in dichloromethane (3ml) was added diphenylsilane (88.6mg, 0.481mmol), tetrakis(triphenylphospine)palladium(0) and zinc chloride (8mg, 0.06mmol) and the resulting mixture was stirred under nitrogen at room temperature for 3 days. The mixture was applied directly to a silca gel column and purified by flash chromatography eluting with a solvent gradient of dichloromethane:pentane (1:3, by volume)and then dichloromethane:pentane (1:2, by volume) to give the title compound (78mg) as a mixture with its enol tautomer as shown by ^{1}H-NMR and as a pale yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = (enol only, signals for diketone not assigned) 2.14 (s, 3H), 3.78 (s, 2H), 7.02 (2, 2H), 7.09 (m, 1H), 16.29 (br. s, 1H).
LRMS (electrospray): m/z [$M-H^+$] 311.

PREPARATION 7

3-(3-Chlorobenzyl)-5-methyl-2,4-hexanedione

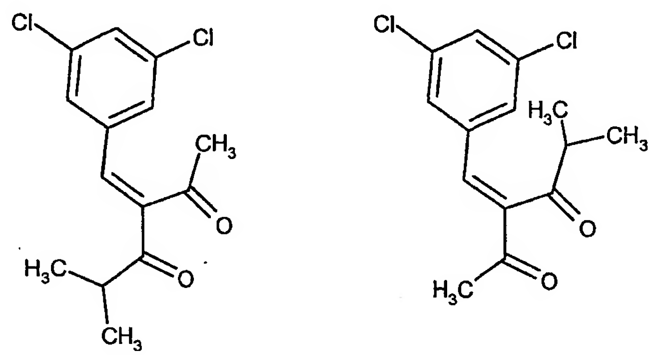


The title compound was prepared by a similar method to that of Preparation 6 using a mixture of the alkenes of Preparation 10, being purified by flash chromatography eluting with pentane:ethyl acetate (3:1, by volume) and being obtained as a mixture with its enol tautomer as shown by ^{1}H-NMR as a yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 0.97-1.01 (m, 6H, diketone and enol), 2.02 and 2.10 (2s, 2x3H, diketone and enol), 2.53 and 2.66 (2m, 2x1H, diketone and enol), 3.07 (m, 2H, diketone), 3.61 (s, 2H, enol), 4.05 (m, 1H, diketone), 7.08 (m, 4H, diketone and enol).

PREPARATION 8

(3*E*)-3-(3,5-Dichlorobenzylidene)-5-methyl-2,4-hexanedione and (3*Z*)-3-(3,5-dichlorobenzylidene)-5-methyl-2,4-hexanedione



A mixture of 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.*, 1980, 2095-6.) (1.84g, 14.33mmol), 3,5-dichlorobenzaldehyde (2.5g, 14.33mmol), glacial acetic acid (214µL, 3.73mmol), piperidine (29µL, 0.29mmol), dry toluene (10.2ml) and powdered 3Å molecular sieves (100mg) was heated under reflux under nitrogen for 24 hours. A Dean-Stark trap was attached to the reaction and heating under reflux was continued for 3 hours, during which time the toluene evaporated from the reaction. The residue was diluted with dichloromethane (80ml) and filtered to remove molecular sieves. The filtrate was washed with water (80ml), dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with pentane:ether (10:1, by volume) to give the less polar title compound (510.6mg) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.19 (d, 6H), 2.29 (s, 3H), 3.19 (heptet, 1H), 7.24 (s, 2H), 7.34 (s, 1H), 7.40 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 302.

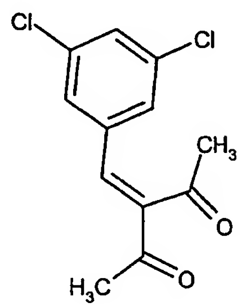
Further elution of the same column gave the more polar title compound (993.3mg) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.05 (d, 6H), 2.40 (s, 3H), 2.58 (heptet, 1H), 7.24 (s, 2H), 7.39 (s, 1H), 7.45 (s, 1H).

LRMS (thermospray): m/z [MNH_4^+] 302.

PREPARATION 9

3-(3,5-Dichlorobenzylidene)-2,4-pentanedione



Glacial acetic acid (0.49ml, 8.6mmol) and piperidine (57μL, 0.6mmol) were added to a stirred solution of 2,4-pentanedione (2.86g, 28.6mmol) and 3,5-dichlorobenzaldehyde (5.00g, 28.6mmol) in toluene (25ml) and the mixture was heated under reflux using a Dean-Stark trap for 18 hours. After cooling, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (10:1, by volume) to give the title compound (6.5g) as a red/brown solid, m.p. 85-87°C.

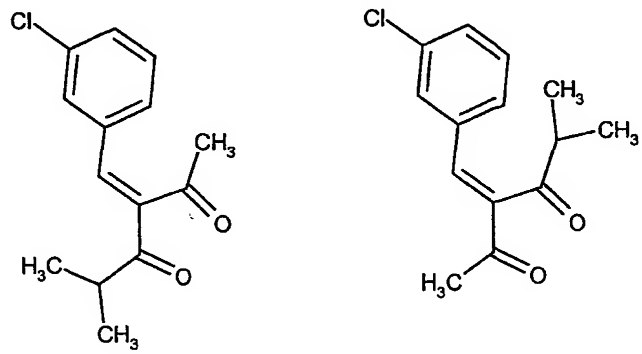
^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.22 (s, 3H), 2.39 (s, 3H), 7.21 (s, 2H), 7.26 (s, 1H), 7.35 (s, 1H).

LRMS (thermospray): m/z [MNH_4^+] 274.

Microanalysis: Found: C, 55.93; H, 3.81. $C_{12}H_{10}Cl_2O_2$ requires C, 56.06; H, 3.92.

PREPARATION 10

(3*E*)-3-(3-Chlorobenzylidene)-5-methyl-2,4-hexanedione and (3*Z*)-3-(3-chlorobenzylidene)-5-methyl-2,4-hexanedione



The title compounds were prepared by a similar method to that of Preparation 9 using 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.,* 1980, 2095-6) and 3-chlorobenzaldehyde and were obtained as yellow oils.

Less polar isomer:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.16 (d, 6H), 2.24 (s, 3H), 3.18 (m, 1H), 7.30 (m, 6H).

LRMS (thermospray): m/z [MNH_4^+] 268.

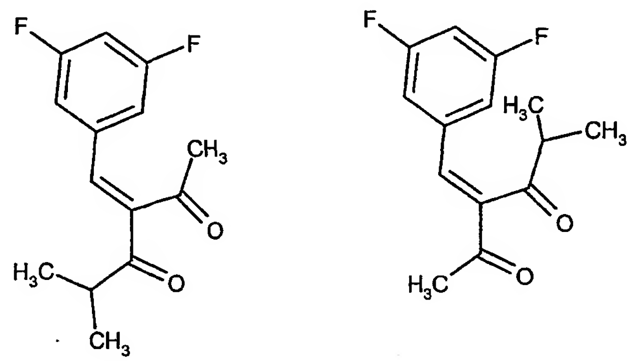
More polar isomer:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.02 (d, 6H), 2.39 (s, 3H), 2.55 (m, 1H), 7.31 (m, 5H), 7.50 (s, 1H).

LRMS (thermospray): m/z [MNH_4^+] 268.

PREPARATION 11

(3*E*)-3-(3,5-Difluorobenzylidene)-5-methyl-2,4-hexanedione and (3*Z*)-3-(3,5-difluorobenzylidene)-5-methyl-2,4-hexanedione



The title compounds were prepared by a similar method to that of Preparation 9 using 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.,* 1980, 2095-6) and 3,5-difluorobenzaldehyde and purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (20:1, by volume) and then pentane:ethyl acetate (10:1, by volume) to give the less polar title compound as a yellow oil.

Less polar isomer:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.15 (d, 6H), 2.27 (s, 3H), 3.19 (heptet, 1H), 6.92 (m, 3H), 7.32 (s,1H).

LRMS (electrospray): m/z [MNH_4^+] 253.

Further elution of the same column gave the more polar title compound as a yellow oil.

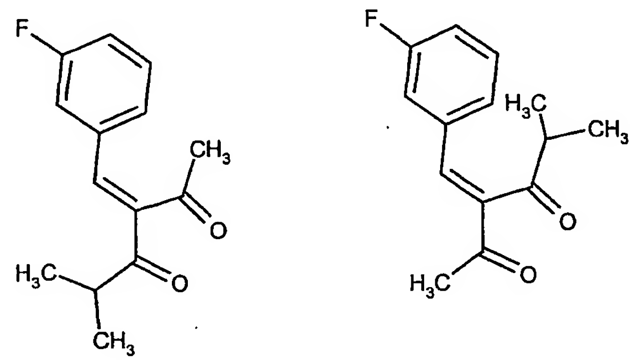
More polar isomer:

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.03 (d, 6H), 2.40 (s, 3H), 2.56 (heptet, 1H), 6.96 (m, 3H), 7.44 (s, 1H).

LRMS (electrospray): m/z [MNH_4^+] 253.

PREPARATION 12

(3*E*)-3-(3-Fluorobenzylidene)-5-methyl-2,4-hexanedione and (3*Z*)-3-(3-fluorobenzylidene)-5-methyl-2,4-hexanedione



The title compounds were prepared by a similar method to that of Preparation 9 using 5-methyl-2,4-hexanedione (*J. Am. Chem. Soc.*, 1980, 2095-6) and 3-fluorobenzaldehyde and purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (20:1, by volume) and then pentane:ethyl acetate (10:1, by volume) to give the less polar title compound as a yellow oil.

Less polar isomer:

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.23 (d, 6H), 2.29 (s, 3H), 3.24 (heptet, 1H), 7.13 (m, 3H), 7.39 (m,1H), 7.44 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 235.

Further elution of the same column gave the more polar title compound as a yellow oil.

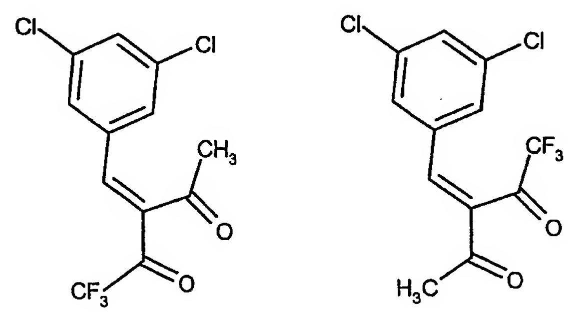
More polar isomer:

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.06 (d, 6H), 2.42 (s, 3H), 2.60 (heptet, 1H), 7.11 (m, 3H), 7.35 (m,1H), 7.55 (s, 1H).

LRMS (thermospray): m/z [MNH_4^+] 235.

PREPARATION 13

(3*E*)-3-(3,5-Dichlorobenzylidene)-1,1,1-trifluoro-2,4-pentanedione and (3*Z*)-3-(3,5-dichlorobenzylidene)-1,1,1-trifluoro-2,4-pentanedione



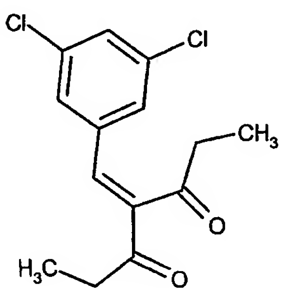
Glacial acetic acid (0.425ml, 7.423mmol) and piperidine (57μL, 0.571mmol) were added to a stirred solution of 1,1,1-trifluoro-2,4-pentanedione (4.40g, 28.55mmol) and 3,5-dichlorobenzaldehyde (5.0g, 28.55mmol) in toluene (20ml) and the mixture was heated under reflux using a Dean-Stark trap for 16h. After cooling the mixture was washed with brine (30ml), dried over magnesium sulphate and concentrated under reduced pressure to give a dark brown oil (9.1g) which was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (10:1, by volume), pentane:ether (5:1, by volume) and then dichloromethane:pentane (1:1, by volume) to give the crude products (4.2g) as a brown oil. The crude products were further purified by flash chromatography on silica gel eluting with a solvent gradient of dichloromethane:pentane (1:4, by volume) and then dichloromethane:pentane (1:3, by volume) to give a mixture of the title compounds (683mg) as shown by thin layer chromatography using dichloromethane:pentane (1:1, by volume), major isomer R_f 0.54, minor isomer R_f 0.17, and as a pale yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.49 (s, 3H), 7.23 (s, 2H), 7.46 (s, 1H), 7.66 (s, 1H).

LRMS (electrospray): m/z [MH^+] 328.

PREPARATION 14

4-(3,5-Dichlorobenzylidene)-3,5-heptanedione



The title compound was prepared by a method similar to that of Preparation 13 using 3,5-heptanedione and was purified by chromatography on silica gel eluting with pentane:ether (10:1, by volume) to give a product which was triturated with pentane to give the title compound as a white solid, m.p. 80-82°C.

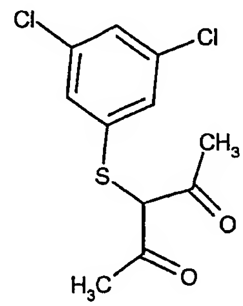
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.16 (m, 6H), 2.50 (q, 2H), 2.73 (q, 2H), 7.22 (s, 2H), 7.37 (m, 2H).

LRMS (thermospray): m/z [MH^+] 285.

Microanalysis: Found: C, 58.97; H, 4.95. $C_{14}H_{14}Cl_2O_2$ requires C, 58.98; H, 4.93.

PREPARATION 15

3-[(3,5-Dichlorophenyl)sulfanyl]-2,4-pentanedione



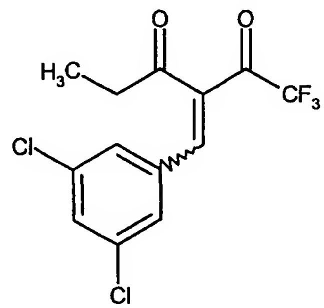
3-Chloro-2,4-pentanedione (723μL, 6.07mmol) and then sodium iodide (910mg, 6.07mmol) were added to a stirred suspension of 3,5-dichlorothiophenol (1.09g, 6.07mmol) and potassium carbonate (923mg, 6.68mmol) in acetone (30ml), at room temperature, in a flask equipped with a calcium chloride drying tube. The mixture became yellow, then orange and finally red accompanied by a slight exotherm and was stirred for 23 hours at room temperature. The mixture was diluted with water (20ml) and concentrated under reduced pressure in a fumehood (Caution: possible residual lachrymator) to remove acetone. The residue was diluted with 2M hydrochloric acid (20ml) and extracted with dichloromethane (1x40ml, 2x20ml). The combined organic phases were washed with brine (20ml), dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to leave an orange solid (1.66g). The crude product was purified by flash chromatography on silica gel eluting with pentane:diethyl ether (99:1, by volume) to give the title compound (807mg) as a yellow solid m.p. 79-81°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.30 (2, 6H), 6.91 (s, 2H), 7.09 (s, 1H).
LRMS (thermospray): m/z [MNH_4^+] 294.

Microanalysis: Found: C, 47.45; H, 3.54; $C_{11}H_{10}Cl_2O_2S$ requires C, 47.67; H, 3.64%.

PREPARATION 16

(3*E* and 3*Z*)-3-(3,5-Dichlorobenzylidene)-1,1,1-trifluoro-2,4-hexanedione

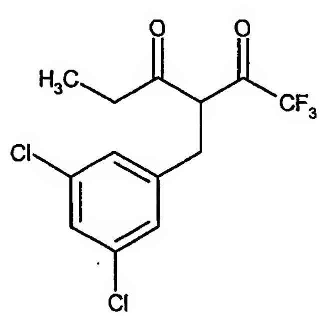


The title compound was prepared by a similar method to that of Preparation 9 using 1,1,1-trifluorohexane-2,4-dione and 3,5-dichlorobenzaldehyde. The crude product was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane gradually changing to pentane:ethyl acetate (5:1, by volume). The product was further purified by flash chromatography eluting with dichloromethane:pentane (1:10, by volume) to afford a mixture of the title compounds (500mg) as a yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.23 (t, 3H), 2.80 (q, 2H), 7.32 (s, 2H), 7.52 (s, 1H), 7.74 (s, 1H).

PREPARATION 17

3-(3,5-Dichlorobenzyl)-1,1,1-trifluoro-2,4-hexanedione

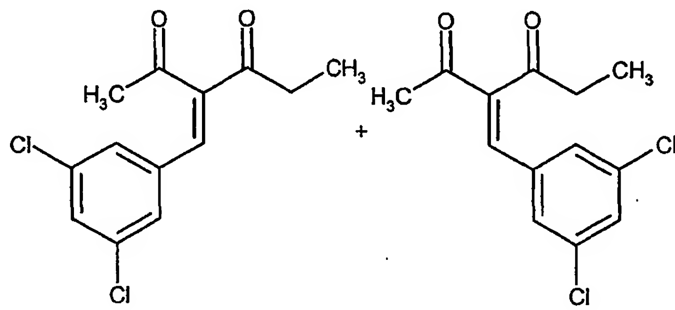


The title compound was prepared by a similar method to that of Preparation 6 using 3-(3,5-dichlorobenzylidene)-1,1,1-trifluoro-2,4-hexanedione of Preparation 16 and was obtained as an oily white solid (180mg).

LRMS (thermospray): m/z [MH^+] 325.

PREPARATIONS 18 AND 19

(3*Z*)-3-(3,5-Dichlorobenzylidene)-2,4-hexanedione and (3*E*)-3-(3,5-Dichlorobenzylidene)-2,4-hexanedione



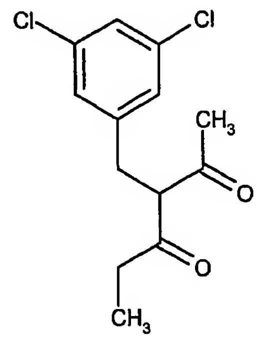
The title compounds were prepared by a similar method to that of Preparation 9 using 2,4-hexanedione and 3,5-dichlorobenzaldehyde. The crude products were purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ether (20:1, by volume) gradually changing to pentane:ether (10:1, by volume) to afford the title compounds as white solids.

Less polar isomer:
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.10 (t, 3H), 2.40 (s, 3H), 2.52 (q, 2H), 7.20 (s, 2H), 7.39 (s, 1H), 7.40 (s, 1H).
Microanalysis: Found: C, 57.07; H, 4.40. $C_{13}H_{12}Cl_2O_2$ requires C, 57.59; H, 4.46.

More polar isomer:
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.16 (t, 3H), 2.29 (s, 3H), 2.77 (q, 2H), 7.29 (s, 2H), 7.39 (s, 1H), 7.40 (s, 1H).
Microanalysis: Found: C, 57.21; H, 4.22. $C_{13}H_{12}Cl_2O_2$ requires C, 57.59; H, 4.46.

PREPARATION 20

3-(3,5-Dichlorobenzyl)-2,4-hexanedione



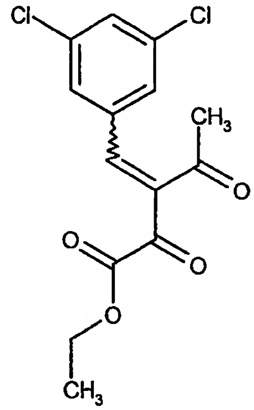
The title compound was prepared by a similar method to that of Preparation 6 using (3*Z*)-3-(3,5-dichlorobenzylidene)-2,4-hexanedione and (3*E*)-3-(3,5-dichlorobenzylidene)-2,4-hexanedione of Preparations 18 and 19 and was obtained as yellow oil (300mg).

^{1}H-NMR (300MHz, $CDCl_3$): (5:4 keto tautomer:enol tautomer) δ = 1.00 (t, 3H, keto), 1.13 (t, 3H, enol), 2.06 (s, 3H, enol), 2.16 (s, 3H, keto), 2.35 and 2.52 (2xm, 2x2H, keto and enol), 3.13 (d, 2H, keto), 3.65 (s, 2H, enol), 3.96 (t, 1H, keto), 7.00 (m, 2x2H, keto and enol), 7.20 (s, 2x1H, keto and enol), 16.87 (s, 1H, enol).

LRMS (thermospray): m/z [MNa^+] 295.

PREPARATION 21

Ethyl (3*E* and 3*Z*)-3-acetyl-4-(3,5-dichlorophenyl)-2-oxo-3-butenoate



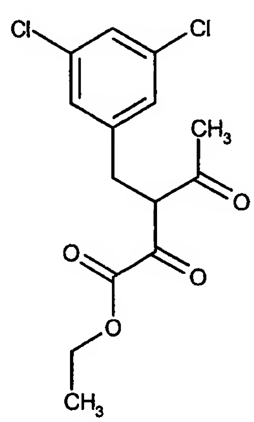
The title compounds were prepared by a similar method to that of Preparation 9 using ethyldioxovalerate and 3,5-dichlorobenzaldehyde and a mixture was obtained (2:3 ratio of isomers, stereochemistry unknown) as an orange oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.25 (m, 3H), 1.29 (m, 3H), 2.37 (s, 3H), 2.44 (s, 3H), 4.21 (q, 2H), 4.30 (q, 2H), 7.21 (s, 2H), 7.22 (s, 2H), 7.40 (s, 1H), 7.41 (s, 1H), 7.68 (s, 2x1H).

LRMS (thermospray): m/z [MNH_4^+] 332.

PREPARATION 22

Ethyl 3-(3,5-dichlorobenzyl)-2,4-dioxopentanoate



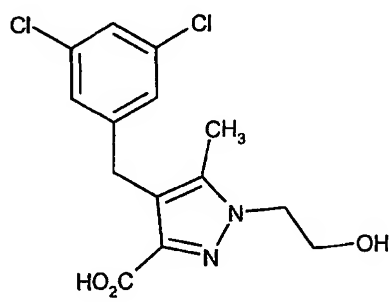
The title compound was prepared by a similar method to that of Preparation 6 using ethyl (3*E* and 3*Z*)-3-acetyl-4-(3,5-dichlorophenyl)-2-oxo-3-butenoate of Preparation 21 and was obtained as a yellow oil (8.2g).

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.19 (m, 3H), 1.31 (m, 3H), 2.12 (s, 3H), 2.20 (s, 3H), 2.98 (dq, 1H, diketone), 3.74 (s, 2H, enol), 4.23 (m, 4H), 7.03 (s, 4H), 7.20 (s, 2H), 15.91 (s, 1H).

LRMS (thermospray): m/z [MH^+] 317.

PREPARATION 23

4-(3,5-Dichlorobenzyl)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid



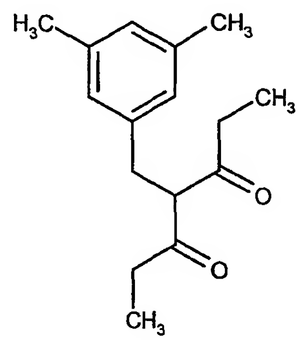
A solution of the ester of Example 84 (1.0g, 2.8mmol) in 1,4-dioxan (14ml) was treated with 1M aqueous sodium hydroxide solution (7ml) and the reaction mixture was stirred at room temperature for 4 hours. The solution was concentrated under reduced pressure. The residue was dissolved in water (25ml) and 2M aqueous hydrochloric acid was added. A precipitate formed and was filtered off to afford the title compound as a white solid (613mg), m.p. 241.2-242.4°C. Further product was obtained from the filtrate by adding methanol and concentrating the solvents under reduced pressure. The residue was dissolved in water and aqueous hydrochloric acid added. A precipitate formed and was filtered off to afford a white solid (108mg).

^{1}H-NMR (300MHz, d_6-DMSO): δ = 2.20 (s, 3H), 3.69 (s, 2H), 4.01 (m, 2H), 4.13 (m, 2H), 7.19 (s, 2H), 7.38 (s, 1H).

LRMS (electrospray): m/z [MH^+] 327.

PREPARATION 24

4-(3,5-Dimethylbenzyl)-3,5-heptanedione



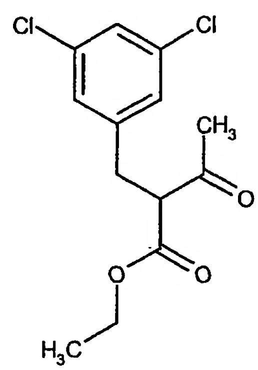
A solution of 3,5-heptanedione (1.24ml, 9.13mmol) in 2-butanone (40ml) was treated with sodium hydride (60% dispersion in oil) (402mg, 10.05mmol) (added in portions) and stirred at room temperature for 10 minutes. Sodium iodide (1.5g, 10.05mmol) and then by 3,5-dimethylbenzyl bromide (2.0g, 10.05mmol) were added to the reaction mixture which was stirred at room temperature for 18 hours. The solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water (x3). The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane followed by cyclohexane:ethyl acetate (40:1, by volume) to afford the title compound as a yellow oil (995mg).

^{1}H-NMR (300MHz, $CDCl_3$): (1.7:1 keto tautomer:enol tautomer) δ = 1.00 (t, 6H, keto), 1.10 (t, 6H, enol), 2.28 (s, 6H, keto), 2.30 (s, 6H, enol), 2.40 (m, 2x4H, keto and enol), 3.10 (d, 2H, keto), 3.61 (s, 2H, enol), 4.00 (t, 1H, keto), 6.77 (s, 2x2H, keto and enol), 6.87 (s, 2x1H, keto and enol), 16.97 (s, 1H, enol).

LRMS (thermospray): m/z [MH^+] 247.

PREPARATION 25

Ethyl 2-(3,5-dichlorobenzyl)-3-oxobutanoate



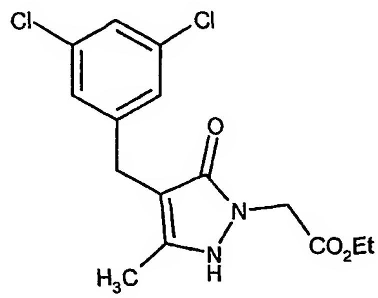
Sodium metal (1.01g, 44mmol) was added to ethanol (100ml) and stirred until all the metal had dissolved. Ethylacetoacetate (15.6g, 111mmol) was added and the reaction mixture was stirred under a nitrogen atmosphere for 10 minutes. 3,5-dichlorobenzyl chloride (7.24g, 40mmol) was added and the reaction mixture was stirred at room temperature for 3 days. The reaction mixture was filtered and the solution was concentrated under reduced pressure. The orange oil was purified by flash chromatography on silica gel eluting with pentane followed by pentane:ethyl acetate (30:1, by volume) to afford the title compound as a colourless oil (6.4g).

^{1}H-NMR (300MHz, $CDCl_3$): (3.3:1 keto tautomer:enol tautomer) δ = 1.23 (t, 2x3H, keto and enol), 2.10 (s, 3H, enol), 2.26 (s, 3H, keto), 3.13 (m, 2H, keto), 3.55 (s, 2H, enol), 3.74 (t, 1H, keto), 4.23 (q, 2H, keto and enol), 7.10 (s, 2H, enol), 7.13 (s, 2H, keto), 7.20 (s, 1H, enol), 7.29 (s, 1H, keto), 12.97 (s, 1H, enol).

LRMS (thermospray): m/z [MNH_4^+] 306, 308.

PREPARATION 26

Ethyl [4-(3,5-dichlorobenzyl)-3-methyl-5-oxo-2,5-dihydro-1*H*-pyrazol-1-yl]acetate



A solution of the β-ketoester of Preparation 25 (100mg, 0.35mmol) in ethanol (2ml) was treated with triethylamine (53µL, 0.38mmol) and by ethyl hydrazinoacetate hydrochloride (54mg, 0.35mmol) and the resulting mixture was heated at 80°C in a sealed Reacti-vial (Trade Mark) for 18 hours. After cooling, the mixture was concentrated under reduced pressure. The residue was partitioned between aqueous saturated sodium hydrogen carbonate solution and dichloromethane. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The resulting solid was purified by flash chromatography on silica gel eluting with methanol:dichloromethane (1:99, by volume) to afford the title compound (40mg) as a white solid, m.p. 183.1-184.4°C.

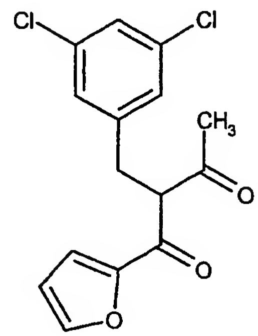
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.20 (t, 3H), 1.97 (s, 3H), 3.45 (brs, 1H), 3.52 (s, 2H), 4.16 (q, 2H), 4.48 (s, 2H), 7.06 (s, 2H), 7.13 (s, 1H).

LRMS (thermospray): m/z [MH^+] 343.

Microanalysis: Found: C, 52.39; H, 4.68; N, 8.08. $C_{15}H_{16}Cl_2N_2O_3$ requires C, 52.49; H, 4.70; N, 8.16%.

PREPARATION 27

2-(3,5-Dichlorobenzyl)-1-(2-furyl)-1,3-butanedione



The title compound was prepared by a similar method to that of Preparation 24 using 1-(2-furyl)-1,3-butanedione except that the reaction mixture was heated at 85°C. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl actetate (10:1, by volume) to afford the title compound (1.8g) as a yellow oil.

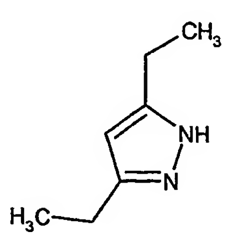
^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.13 (s, 3H), 3.17 (d, 2H), 4.54 (t, 1H), 6.57 (m, 1H), 7.05 (s, 2H), 7.12 (s, 1H), 7.22 (m, 1H), 7.60 (m, 1H).

LRMS (thermospray): m/z [MH^+] 312.

Microanalysis: Found: C, 57.85 H, 4.23. $C_{15}H_{12}Cl_2O_3$ requires C, 57.90; H, 3.89.

PREPARATION 28

3,5-Diethyl-1*H*-pyrazole



A solution of 3,5-heptanedione (10.0g, 0.078mmol) in ethanol (40ml) was treated dropwise with hydrazine hydrate (4.2ml, 0.086mmol) at room temperature

producing an exotherm that was cooled by use of an ice bath. After the addition was complete the reaction mixture was allowed to warm to room temperature. The solution was concentrated under reduced pressure. The oil was partitioned between dichloromethane and brine. The aqueous layer was extracted with dichloromethane (x2). The combined organic phases were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford the title compound (9.66g) as a pale yellow oil that partly solidified on standing.

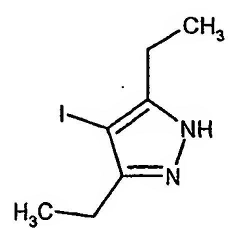
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.22 (t, 6H), 2.60 (q, 4H), 5.85 (s, 1H).

LRMS (thermospray): m/z [MH^+] 124.

Microanalysis: Found: C, 67.00 H, 9.85; N, 22.37. $C_7H_{12}N_2$ requires C, 66.73; H, 9.76; N, 22.23%.

PREPARATION 29

3,5-Diethyl-4-iodo-1*H*-pyrazole



A solution of the pyrazole of Preparation 28 (2.0g, 16.1mmol) in dichloromethane (80ml) was cooled to 0°C and treated with N-iodosuccinimide (3.97g, 17.7mmol) and the resulting mixture was stirred for 18 hours. Further N-iodosuccinimide (360mg, 1.77mmol) was added and the solution was stirred for a further hour. The reaction mixture was washed with saturated aqueous sodium hydrogencarbonate solution. The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a solvent gradient of pentane:ethyl actetate (4:1, by volume) gradually changing to pentane:ethyl actetate (2:1, by volume). Methanol was added to the resulting

solid, which was collected by filtration and the filtrate was concentrated under reduced pressure. The resulting oil was dissolved in dichloromethane and washed with 10% aqueous sodium metabisulphite solution. The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford the title compound (3.3g) as a white solid.

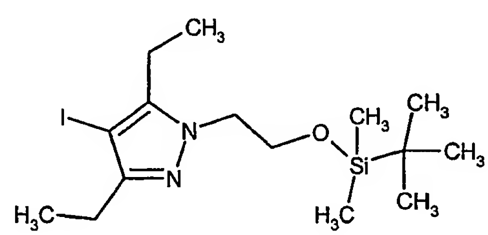
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.26 (t, 6H), 2.68 (q, 4H).

LRMS (thermospray): m/z [MH^+] 251.

Microanalysis: Found: C, 33.41 H, 4.38; N, 11.14. $C_7H_{11}N_2I$ requires C, 33.62; H, 4.43; N, 11.20%.

PREPARATION 30

1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,5-diethyl-4-iodo-1*H*-pyrazole



A solution of the pyrazole of Preparation 29 (3.3g, 13.2mmol) in dimethylformamide (70ml) was cooled to 0°C and treated with sodium hydride (60% dispersion in oil) (580mg, 14.5mmol). After 20 minutes sodium iodide (2.17g, 14.5mmol) and (2-bromoethoxy)-tert-butyldimethylsilane (3.11ml, 14.5mmol) were added and the resulting mixture was stirred at 0°C for 30 minutes. The reaction mixture was allowed to warm to room temperature and was stirred for 18 hours at this temperature. Further (2-bromoethoxy)-tert-butyldimethylsilane (2x2.8ml) was added over a 2 hour period. The reaction mixture was then heated at 50°C for 1 hour. After cooling to 0°C, the reaction mixture was diluted with water (2ml) and evaporated under reduced pressure. The resulting solid was partitioned between dichloromethane and water. The organic layer was dried over anhydrous magnesium sulphate, filtered and

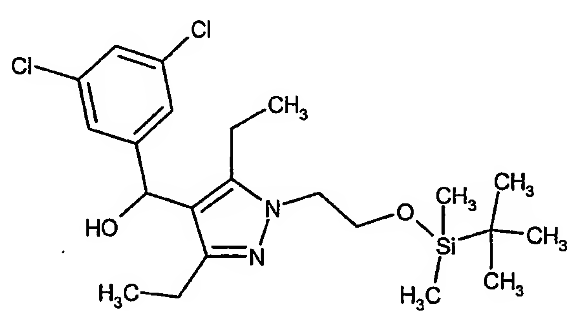
evaporated under reduced pressure. The resulting oil was then dissolved in ethyl acetate and washed with brine (x4). The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a solvent gradient of cyclohexane gradually changing to cyclohexane:ethyl actetate (10:1, by volume) to afford the title compound (2.6g) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = -0.10 (s, 6H), 0.80 (s, 9H), 1.16 (t, 3H), 1.23 (t, 3H), 2.60 (q, 2H), 2.74 (q, 2H), 3.97 (t, 2H), 4.16 (t, 2H).

LRMS (thermospray): m/z [MH^+] 409.

PREPARATION 31

[1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,5-diethyl-1*H*-pyrazol-4-yl](3,5-dichlorophenyl)methanol



A solution of the iodo-pyrazole (500mg, 1.22mmol) of Preparation 30 in tetrahydrofuran (7.5ml) at 0°C was treated with iso-propylmagnesium chloride (2M in diethylether) (725μL, 1.46mmol). After 1 hour, 3,5-dichlorobenzaldehyde (252mg, 1.46mmol) was added and after a further 10 minutes the reaction mixture was allowed to warm to room temperature. After 3 days saturated aqueous ammonium chloride solution was added to the reaction mixture which was then extracted with dichloromethane. The organic extract was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel

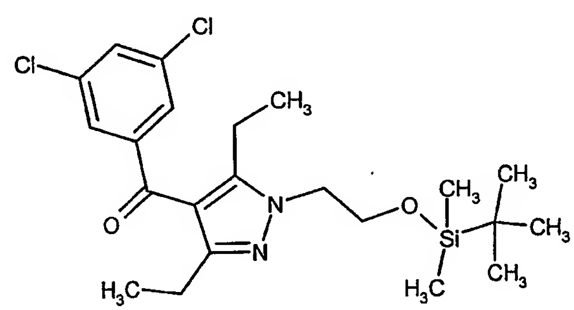
eluting with a solvent gradient of pentane:ethyl actetate (5:1, by volume) gradually changing to pentane:ethyl actetate (2:1, by volume) to afford the title compound (190mg) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = -0.10 (s, 6H), 0.80 (s, 9H), 1.03 (t, 3H), 1.16 (t, 3H), 2.58 (m, 4H), 4.00 (t, 2H), 4.10 (t, 2H), 5.80 (s, 1H), 7.39 (m, 3H).

LRMS (thermospray): m/z [MH^+] 457.

PREPARATION 32

[1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,5-diethyl-1*H*-pyrazol-4-yl](3,5-dichlorophenyl)methanone



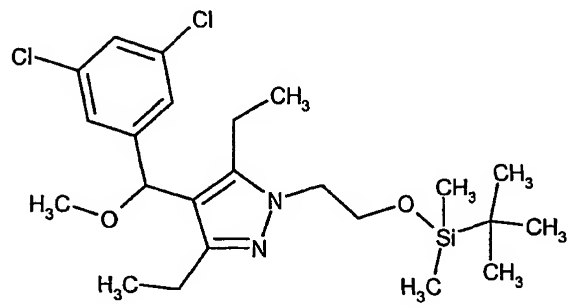
A solution of the alcohol of Preparation 31 (75mg, 0.16mmol) in dichloromethane (2ml) was treated with *N*-methylmorpholine *N*-oxide (28mg, 0.24mmol) and tetra-n-propylammonium perruthenate (VII) (3mg, 0.008mmol) and stirred at room temperature, under a nitrogen atmosphere for 2 hours. The reaction was diluted with dichloromethane and washed with aqueous sodium sulphite solution (x3). The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude material was pre-absorbed onto silica and purified by flash chromatography on silica gel eluting with a solvent gradient of pentane gradually changing to pentane:ethyl actetate (10:1, by volume) to afford the title compound (73mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = -0.03 (s, 6H), 0.84 (s, 9H), 1.13 (m, 6H), 2.48 (m, 2H), 2.77 (m, 2H), 4.06 (m, 2H), 4.19 (m, 2H), 7.29 (s, 1H), 7.58 (s, 2H).

LRMS (thermospray): m/z [MH$^+$] 455.

PREPARATION 33

1-(2-{[*Tert*-butyl(dimethyl)silyl]oxy}ethyl)-4-[(3,5-dichlorophenyl)(methoxy)methyl]-3,5-diethyl-1*H*-pyrazole



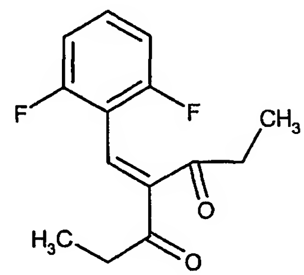
A solution of the alcohol of Preparation 31 (75mg, 0.16mmol) in dimethylformamide (1ml) was treated with sodium hydride (60% dispersion in oil) (7mg, 0.18mmol) and stirred under a nitrogen atmosphere, at room temperature for 30 minutes. Methyl iodide (11μL, 0.18mmol) was added and the resulting mixture was stirred for 7 days. The solution was concentrated under reduced pressure. The residue was partitioned between dichloromethane and saturated aqueous sodium hydrogencarbonate solution. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl actetate (10:1, by volume) to afford the title compound (30mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = -0.10 (m, 6H), 0.81 (s, 9H), 1.03 (t, 3H), 1.16 (t, 3H), 2.58 (m, 4H), 3.39 (s, 3H), 4.03 (m, 2H), 4.13 (m, 2H), 5.20 (s, 1H), 7.29 (s, 3H).

LRMS (thermospray): m/z [MH$^+$] 471.

PREPARATION 34

4-(2,6-Difluorobenzylidene)-3,5-heptanedione



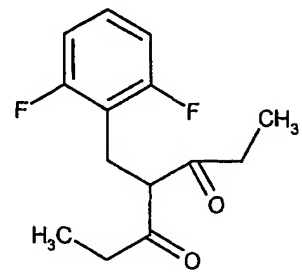
A mixture of 3,5-heptanedione (1.36ml, 10mmol), 2,6-difluorobenzaldehyde (1.08ml, 10mmol), piperidine (20µL, 0.2mmol), glacial acetic acid (149µL, 2.6mmol), molecular sieves and toluene (7ml) was heated at 70°C, under a nitrogen atmosphere for 3 hours. Further 2,6-difluorobenzaldehyde (540µL, 5mmol) was added and the resulting mixture was stirred at 70°C for a further 7 hours. After cooling, the molecular sieves were filtered off. The filtrate was concentrated under reduced pressure. The residue was partitioned between dichloromethane and water. The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with pentane:dichloromethane (4:1, by volume) and then with a solvent gradient of pentane:diethylether (20:1, by volume) gradually changing to pentane:diethylether (10:1, by volume) to afford the title compound (775mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.11 (t, 3H), 1.20 (t, 3H), 2.63 (q, 2H), 2.80 (q, 2H), 6.95 (m, 2H), 7.40, (s, 1H), 7.65 (m, 1H).

LRMS (electrospray): m/z [MH^+] 253.

PREPARATION 35

4-(2,6-Difluorobenzyl)-3,5-heptanedione



The title compound was prepared by the same method as Preparation 2 using the alkene of Preparation 34 and was obtained as a white solid, m.p. 55-56°C.

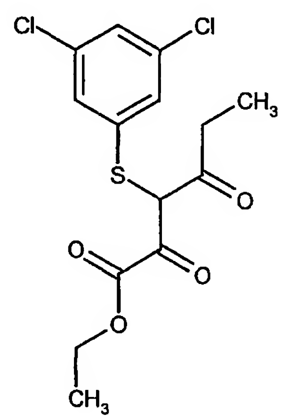
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.00 (t, 6H), 2.46 (m, 4H), 3.20 (d, 2H), 4.03 (t, 1H), 6.84 (m, 2H), 7.18 (m, 1H).

LRMS (thermospray): m/z [MNH_4^+] 272.

Microanalysis: Found: C, 66.22 H, 6.34. $C_{14}H_{16}F_2O_2$ requires C, 66.13; H, 6.34.

PREPARATION 36

Ethyl 3-[(3,5-dichlorophenyl)sulfanyl]-2,4-dioxohexanoate



A solution of ethyl 3-chloro-2,4-dioxohexanoate (EP117082 A2) (7.10g, 34.4mmol) in acetone (175ml) was treated with 3,5-dichlorothiophenol (6.16g,

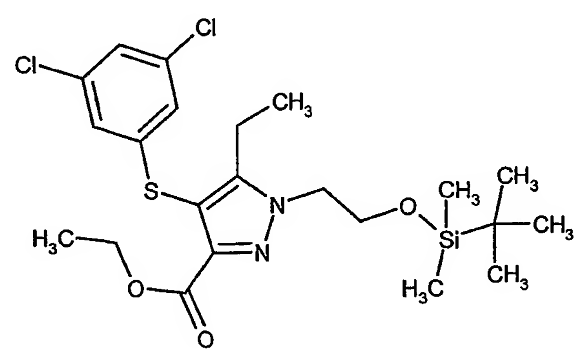
34.4mmol), potassium carbonate (5.22g, 37.8mmol) and sodium iodide (5.16g, 34.4mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with water (70ml) and concentrated under reduced pressure. The residue was diluted with 2M aqueous hydrochloric acid (70ml) and extracted with dichloromethane (3x150ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a solvent gradient of cyclohexane:ethyl acetate (3:1, by volume) gradually changing to cyclohexane:ethyl acetate (1:1, by volume) to afford the title compound (12.3g) as a red oil .

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.14 (t, 3H), 1.19 (t, 3H), 2.70 (q, 2H), 4.28 (q, 2H), 7.02 (s, 2H), 7.14 (s, 1H), 16.15 (brs, 1H).

LRMS (electrospray): m/z [$M-H^+$] 347.

PREPARATION 37

<u>Ethyl 1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1*H*-pyrazole-3-carboxylate</u>



To a solution of Example 46 (1.03g, 2.65mmol) in dimethylformamide (5ml) was added imidazole (361mg, 5.30mmol), followed by tert-butyldimethylchlorosilane (600mg, 3.97mmol). The solution was stirred at room temperature for 4 days. The reaction mixture was partitioned between ethyl acetate and water and the aqueous phase was further extracted with ethyl acetate. The combined organic

phases were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give a yellow oil. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (20:1, by volume), followed by cyclohexane:ethyl actetate (5:1, by volume) to afford the title compound (1.1g) as a white powder, m.p. 83-84^{o}C.

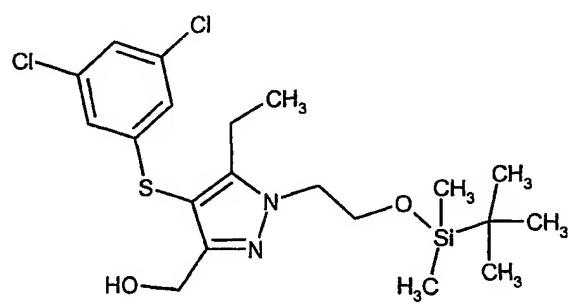
^{1}H-NMR (400MHz, $CDCl_3$): δ = -0.08 (s, 6H), 0.80 (s, 9H), 1.12 (t, 3H), 1.22 (t, 3H), 2.84 (q, 2H), 4.04 (t, 2H), 4.32 (m, 4H), 6.91 (s, 2H), 7.04 (s, 1H).

LRMS (thermospray): m/z [MH^+] 503.

Microanalysis: Found: C, 52.35; H, 6.43; N, 5.46. $C_{22}H_{32}Cl_2N_2O_3SSi$ requires C, 52.47; H, 6.41; N, 5.56%.

PREPARATION 38

{1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1*H*-pyrazol-3-yl}methanol



A stirred solution of the pyrazole (1.11g, 2.21mmol) of Preparation 37 in THF (20ml) was cooled to –78^{o}C and treated dropwise with a solution of lithium aluminium hydride in THF (2.65ml of a 1.0M solution). After 1 hour the mixture was warmed to 0^{o}C and after a further 2 hours water (2ml) was carefully added. The reaction mixture was partitioned between ethyl acetate and water and then the aqueous phase was further extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give a colourless oil. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl

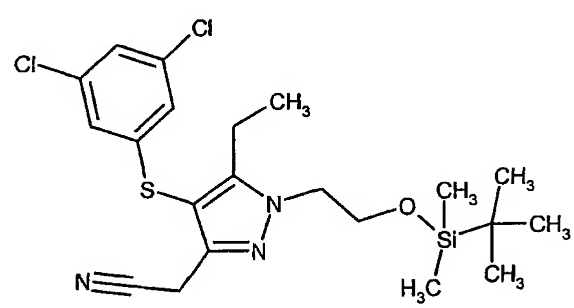
acetate (10:1, by volume) followed by cyclohexane:ethyl actetate (5:1, by volume) to afford the title compound (891mg) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = -0.08 (s, 6H), 0.80 (s, 9H), 1.04 (t, 3H), 2.00 (t, 1H), 2.75 (q, 2H), 4.00 (t, 2H), 4.18 (t, 2H), 4.60 (d, 2H), 6.84 (s, 2H), 7.02 (s, 1H).

LRMS (thermospray): m/z [MH$^+$] 461.

PREPARATION 39

{1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1*H*-pyrazol-3-yl}acetonitrile



To a stirred solution of the alcohol (340mg, 0.74mmol) of Preparation 38 in dichloromethane (6ml) was added triethylamine (113μl, 0.81mmol) and methanesulfonyl chloride (63μl, 0.81mmol). After 1 hour at room temperature the reaction mixture was partitioned between dichloromethane and water and then the aqueous phase was further extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give a colourless oil. This crude mesylate was dissolved in dimethylformamide (5ml) and sodium cyanide (109mg, 2.22mmol) was added. The reaction mixture was heated at 60°C for 1 hour. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane and water. The organic phase was separated, washed with water and brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure

to give a yellow oil. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (3:1, by volume) to afford the title compound (240mg) as a colourless oil.

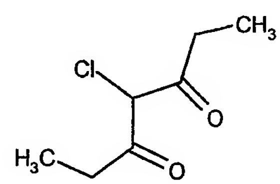
^{1}H-NMR (400MHz, $CDCl_3$): δ = -0.04 (s, 6H), 0.82 (s, 9H), 1.11 (t, 3H), 2.78 (q, 2H), 3.62 (s, 2H), 4.02 (t, 2H), 4.20 (t, 2H), 6.82 (s, 2H), 7.10 (s, 1H).

LRMS (electrospray): m/z [M+Na$^+$] 492.

Accurate Mass: Found: 470.1250 [MH$^+$]; $C_{21}H_{30}Cl_2N_3OSSi$ requires 470.1250 [MH$^+$].

PREPARATION 40

4-Chloro-3,5-heptanedione



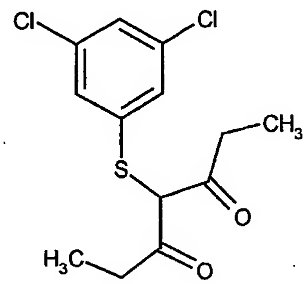
Chlorotrimethylsilane (29.7ml, 0.234mol) was added dropwise to a stirred pale yellow solution of tetrabutylammonium bromide (1.26g, 3.9mmol) in dry acetonitrile (116ml) at room temperature under nitrogen. The resulting solution was cooled in ice and 3,5-heptanedione (10.6ml, 78.0mmol) and then dry dimethylsulphoxide (16.6ml, 0.234mol) were added dropwise over 5 minutes producing a yellow solution which was allowed to warm slowly to room temperature, with stirring, over 4 hours. The mixture was diluted with water (1litre), stirred for 10min and then extracted with ether (1x500ml, 2x250ml). The combined ether layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow oil. The crude product was purified by distillation under reduced pressure to afford the title compound (5.5g) as a pale yellow oil, b.p. 102-105°C/54mmHg containing *ca.* 10% 4,4-dichloro-3,5-heptanedione as estimated by microanalysis.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.12 (t, 6H), 2.59 (q, 4H), 4.77 (s, 0.2H, diketone), 15.50 (s, 0.8H, enol).

LRMS (thermospray): m/z [MNH_4^+] 180 for title compound and 214 for dichlorinated impurity.

PREPARATION 41

4-[(3,5-Dichlorophenyl)sulfanyl]-3,5-heptanedione



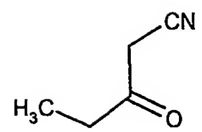
To a stirred solution of the chlorodiketone (1.0g) of Preparation 40 in acetone (30ml) was added 3,5-dichlorothiophenol (1.1g, 6.15mmol), potassium carbonate (900mg, 6.77mmol) and sodium iodide (900mg, 6.15mmol). After 18 hours the reaction mixture was diluted with water (20ml) and the acetone was removed under reduced pressure. The residue was partitioned between 2M HCl and dichloromethane. The aqueous phase was separated and further extracted with dichloromethane. The combined organic phases were washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow oil (2g). The crude product was used without further purification.

^{1}H-NMR (400MHz, $CDCl_3$): enol tautomer, δ = 1.03 (t, 6H), 2.62 (m, 4H), 6.91 (s, 2H), 7.08 (s, 1H).

LRMS (electrospray): m/z [$M-H^+$] 303.

PREPARATION 42

3-Oxopentanenitrile

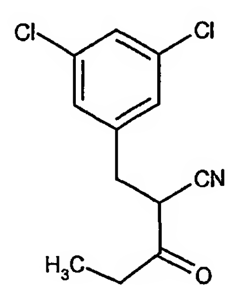


A mixture of ethyl propionate (20g, 196mmol) and sodium ethoxide (13.3g, 196mmol) was heated at 80°C. After 15 mins acetonitrile (13.3ml, 255mmol) was added and the mixture was heated at 120°C. After 13 hours the reaction mixture was cooled and acidified to pH2 using 1M HCl. The volatile reaction components were removed under reduced pressure and the mixture was extracted using dichloromethane. The organic phase was separated, washed with water, washed with brine and concentrated under reduced pressure to give a brown oil (10g). The crude product was used without further purification.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.01 (t, 3H), 2.56 (q, 2H), 3.43 (s, 2H).

PREPARATION 43

2-(3,5-Dichlorobenzyl)-3-oxopentanenitrile



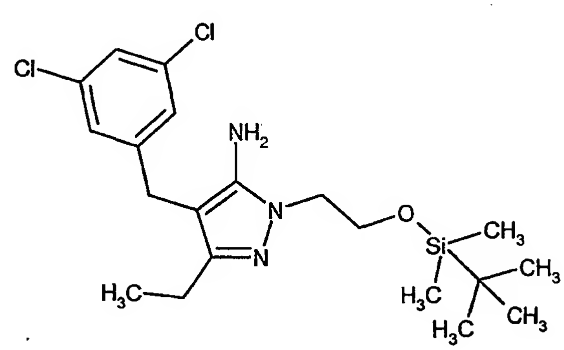
A stirred solution of the nitrile (11.3g, 117mmol) of Preparation 42 and 3,5-dichlorobenzylchloride (27.8g, 117mmol) in N, N-dimethylformamide (200ml) was cooled to 0°C before addition of sodium hydride (60% $^{w}/_{w}$ suspension in mineral oil) (9.3g, 234mmol) portionwise. After 2 hours the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (500ml) and the resulting mixture was extracted with ethyl acetate. The organic

phase was separated and twice washed with water, washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to give a dark oil. The crude product was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (9:1, by volume) to afford the title compound (7g) as a white solid, m.p. 59-60°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.04 (t, 3H), 2.68 (m, 2H), 3.02 (m, 1H), 3.18 (m, 1H), 3.58 (m, 1H), 7.10 (s, 2H), 7.25 (s, 1H).
LRMS (thermospray): m/z [$M+NH_4^+$] 273.
Microanalysis: Found: C, 56.06; H, 4.33; N, 5.41. $C_{12}H_{11}Cl_2NO$ requires C, 56.27; H, 4.33; N, 5.47%.

PREPARATION 44

1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-4-(3,5-dichlorobenzyl)-3-ethyl-1*H*-pyrazol-5-amine



To a solution of the pyrazole of Example 89 (3.0g, 9.6mmol) in dimethylformamide (20ml) was added imidazole (850mg, 12.5mmol), followed by tert-butyldimethylchlorosilane (1.58g, 10.6mmol). The solution was stirred at room temperature for 20 hours. The reaction mixture was partitioned between diethyl ether and aqueous sodium carbonate and the aqueous phase was separated and further extracted with diethyl ether. The combined organic phases were washed with water, washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with

dichloromethane:methanol:ammonia (95:5:0.5, by volume) to afford the title compound (4.0g) as a colourless oil.

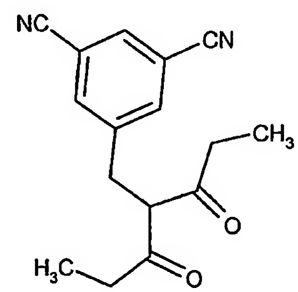
^{1}H-NMR (400MHz, $CDCl_3$): δ = -0.08 (s, 6H), 0.79 (s, 9H), 1.11 (t, 3H), 2.42 (q, 2H), 3.58 (s, 2H), 3.63 (s, 2H), 3.87 (t, 2H), 4.07 (t, 2H), 7.00 (s, 2H), 7.14 (s, 1H).

LRMS (thermospray): m/z [MH^+] 428.

Microanalysis: Found: C, 55.92; H, 7.28; N, 9.74. $C_{20}H_{31}Cl_2N_3OSi$ requires C, 56.06; H, 7.29; N, 9.81%.

PREPARATION 45

5-(3-Oxo-2-propionylpentyl)isophthalonitrile



Sodium hydride (60% dispersion in oil, 116mg, 2.90mmol) was added to a stirred solution of 3,5-heptanedione (358μl, 2.64mmol) in 2-butanone (5ml) at room temperature under nitrogen. After evolution of hydrogen had ceased, sodium iodide (396mg, 2.64mmol) and then a solution of 5-bromomethyl-isophthalonitrile (J.Org.Chem., 1990, *55* (3), 1040-1043) (584mg, 2.64mmol) in 2-butanone (6ml) was added and the mixture was heated at reflux for 6 hours. After cooling, the mixture was quenched with water (1ml) and the 2-butanone was removed under reduced pressure. The residue was partitioned between water (40ml) and dichloromethane (40ml) and the organic layer was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with a solvent gradient starting with pentane:ethyl acetate (10:1, by volume) and

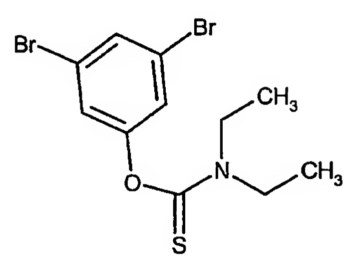
finishing with pentane:ethyl acetate (3:1, by volume) to give the title compound (370mg) as a white solid m.p. 67-69°C.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.1 (6H, m), 2.44 (4H, m), 3.20 (2H, d, keto), 3.79 (2H, s, enol), 3.98 (1H, t, keto), 7.61 (2H, s), 7.8 (1H, s), 17.11 (1H, s, enol).
LRMS (electrospray): m/z [M-H$^+$] 267.

Microanalysis: Found: C, 71.35; H, 6.02; N, 10.41. $C_{16}H_{16}N_2O_2$ requires C, 71.62; H, 6.01; N, 10.44%.

PREPARATION 46

O-(3,5-Dibromophenyl) diethylthiocarbamate

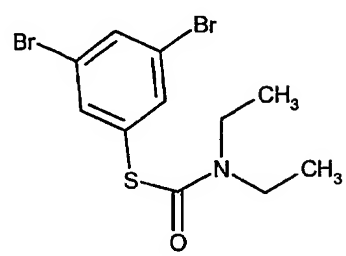


A solution of 3,5-dibromophenol (prepared according to Recl. Trav. Chim. Pays-Bas. 1908, *27*, 30) (10.08g, 40mmol) and diethylthiocarbamyl chloride (7.9g, 52 mmol) in 1-methyl-2-pyrrolidinone (80ml) was cooled to 0°C under an atmosphere of nitrogen. Sodium hydride (60% dispersion in mineral oil, 1.92g, 48 mmol) was added portionwise with stirring. The mixture was allowed to warm to 20°C and stirred under nitrogen for two hours. The mixture was partitioned between diethyl ether (250ml) and water (350ml) and the aqueous layer was further extracted with diethyl ether (250ml then 100ml). The organic layers were combined, washed with water (150ml) and brine (150ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow solid. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:pentane (1:1, by volume) to provide the title compound (13.4g) as a white solid, m.p. 72-74°C.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.27 (m, 6H), 3.62 (q, 2H), 3.84 (q, 2H), 7.17 (d, 2H), 7.51 (d, 1H).
Microanalysis: Found: C, 35.99; H, 3.54; N, 3.73. $C_{11}H_{13}Br_2NOS$ requires C, 35.99; H, 3.57; N, 3.82%.

PREPARATION 47

S-(3,5-dibromophenyl) diethylthiocarbamate

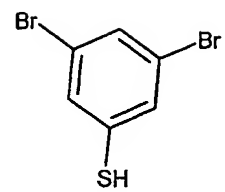


O-(3,5-dibromophenyl) diethylthiocarbamate (13.24g, 36.1 mmol) (Preparation 46) was heated to 200°C, with stirring, under an atmosphere of nitrogen, for 15 hours to leave a yellow oil. A sample of this material (1g) was purified by flash chromatography on silica gel eluting with pentane:dichloromethane (1:1, by volume) to provide the title compound (700mg) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.26 (m, 6H), 3.43 (q, 4H), 7.62 (s, 2H), 7.68 (s, 1H).
Microanalysis: Found: C, 35.92; H, 3.47; N, 3.69. $C_{11}H_{13}Br_2NOS$ requires C, 35.99; H, 3.57; N, 3.82%.

PREPARATION 48

3,5-Dibromobenzenethiol

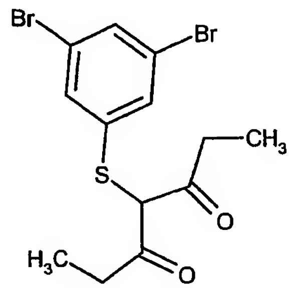


Sodium hydroxide (1.96g, 49mmol) was added to a solution of *S*-(3,5-dibromophenyl) diethylthiocarbamate (12g, 32.7mmol) (Preparation 47) in methanol (33ml) and the mixture was heated at reflux for 15 hours. The mixture was cooled to 20°C and concentrated under reduced pressure. The residue was partitioned between dichloromethane (90ml) and water (250ml) and the aqueous layer was further extracted with dichloromethane (90ml). The combined organic layers were washed with a solution of sodium hydroxide (1N, 100ml). The combined aqueous layers were cooled to 0°C and the pH was adjusted to 2 by the addition of concentrated hydrochloric acid, giving a white suspension. This suspension was extracted with dichloromethane (2x250ml) and the combined extracts were washed with brine (25ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave the title compound as a yellow solid (6.7g).

^{1}H-NMR (300MHz, $CDCl_3$): δ = 3.55 (s, 1H), 7.36 (m, 2H), 7.46 (s, 1H).
LRMS (electrospray): m/z [M-H] 267.
Microanalysis: Found: C, 27.01; H, 1.42. $C_6H_4Br_2S$ requires C, 26.89; H, 1.50%.

PREPARATION 49

4-[(3,5-Dibromophenyl)sulfanyl]-3,5-heptanedione



Potassium carbonate (1.9g, 14mmol) was added to a solution of 3,5-dibromobenzenethiol (2.84g, 10.5mmol) (Preparation 48) and 4-chloroheptane-3,5-dione (1.7g, 10.5mmol) (Preparation 40) in acetone (12ml) producing a white suspension. The mixture was stirred at room temperature for 15 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (100ml) and 1N hydrochloric acid (70ml). The aqueous layer was extracted with further dichloromethane (2x100ml). The combined organic layers were washed with brine (50ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a pink oil. The crude product was purified by flash chromatography on silica gel eluting with pentane:dichloromethane (1:1, by volume) to provide the title compound (3g) as a pink oil.

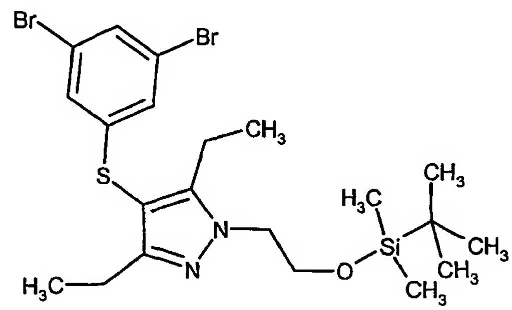
^{1}H-NMR (300MHz, $CDCl_3$): δ = 1.13 (m, 6H), 2.7 (m, 4H), 7.12 (s, 2H), 7.42 (s, 1H), 17.70 (s, 1H).

LRMS (thermospray): m/z [MNH_4^+] 412.

LRMS (electrospray): m/z [M-H] 393.

PREPARATION 50

1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-4-[(3,5-dibromophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazole



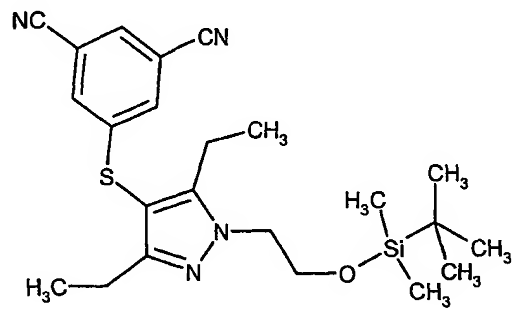
A solution of 2-{4-[(3,5-dibromophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol (1.3g, 3mmol) (Example 93) in dimethylformamide (3ml) was treated with imidazole (270mg, 4mmol) and *tert*-butyl(chloro)dimethylsilane (500mg, 3.3mmol) and stirred at 20°C for 15 hours. The mixture was partitioned between diethyl ether (70ml) and citric acid solution (5% weight:volume in water, 150ml). The aqueous layer was further extracted with diethyl ether (70ml) and the combined organic layers were washed with brine (2x70ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with pentane:dichloromethane (1:1, by volume) to provide the title compound (1.2g) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = -0.05 (s, 6H), 0.84 (s, 9H), 1.10 (t, 3H), 1.19 (t, 3H), 2.58 (q, 2H), 2.75 (q, 2H), 4.04 (m, 2H), 4.18 (m, 2H), 7.05 (s, 2H), 7.35 (s, 1H).

LRMS (electrospray): m/z [MH^+] 549.

PREPARATION 51

5-{[1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]sulfanyl}isophthalonitrile



A solution of 1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4-[(3,5-dibromophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazole (500mg, 0.9mmol) (Preparation 50) in dimethylformamide (2ml) was treated with zinc cyanide (130mg, 1.1mmol), 1,1'-bis(diphenylphosphino)ferrocene (65mg, 0.12mmol) and tris(dibenzylideneacetone)dipalladium (92mg, 0.1mmol) and the resulting brown suspension was heated at 100°C for $2^1/_2$ days. After cooling the mixture was diluted with water (70ml) and extracted with ethyl acetate (2x60ml). The combined organic layers were washed with water (20ml) and brine (30ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a brown oil. The crude product was purified by flash chromatography on silica gel eluting with pentane:dichloromethane (1:1, by volume) then dichloromethane and finally with dichloromethane:ethyl acetate (19:1, by volume) to provide the title compound (180mg) as a brown oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ = -0.03 (s, 6H), 0.84 (s, 9H), 1.10 (t, 3H), 1.18 (t, 3H), 2.56 (q, 2H), 2.72 (q, 2H), 4.06 (m, 2H), 4.20 (m, 2H), 7.43 (s, 2H), 7.60 (s, 1H).

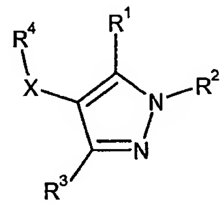
LRMS (thermospray): m/z [MH^+] 441.

PHARMACOLOGICAL ACTIVITY

All the compounds of the Examples were tested for their ability to inhibit HIV-1 reverse transcriptase by the method described on page 36 and all had an IC_{50} of less than 100 micromolar.

CLAIMS

1. The use of a compound of the formula



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

either (i) R^1 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, -CN, $-OR^7$, $-OR^8$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5CO$-(C_1-C_6 alkylene)-OR^5, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6, said C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, $-OR^5$, $-OR^8$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^8R^9$, $-NR^5COR^5$, $-NR^5COR^6$, $-NR^5COR^8$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6, and

R^2 is H or -Y-Z,

or, (ii) R^1 and R^2, when taken together, represent unbranched C_3-C_4 alkylene, optionally wherein one methylene group of said C_3-C_4 alkylene is replaced by an oxygen atom or a nitrogen atom, said nitrogen atom being optionally substituted by R^5 or R^8;

Y is a direct bond or C_1-C_3 alkylene;

Z is R^{10} or, where Y is C_1-C_3 alkylene, Z is $-NR^5COR^{10}$, $-NR^5CONR^5R^{10}$, $-NR^5CONR^5COR^{10}$ or $-NR^5SO_2R^{10}$;

R^3 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, -CN, halo, $-OR^7$, $-CO_2R^5$,

$-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6, said C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, $-OR^5$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5COR^5$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6;

R^4 is phenyl or pyridyl, each being optionally substituted by R^6, halo, -CN, C_1-C_6 alkyl, fluoro-(C_1-C_6)-alkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy;

each R^5 is independently either H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, fluoro-(C_1-C_6)-alkyl, phenyl or benzyl, or, when two such groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl and morpholinyl being optionally substituted by C_1-C_6 alkyl or C_3-C_7 cycloalkyl and said piperazinyl and homopiperazinyl being optionally substituted on the nitrogen atom not taken together with the two R^5 groups to form the ring by $-COR^7$ or $-SO_2R^7$;

R^6 is a four to six-membered, aromatic, partially unsaturated or saturated heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s), said heterocyclic group being optionally substituted by $-OR^5$, $-NR^5R^5$, -CN, oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, $-COR^7$ or halo;

R^7 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, fluoro-(C_1-C_6)-alkyl, phenyl or benzyl;

R^8 is C_1-C_6 alkyl substituted by phenyl, phenoxy, pyridyl or pyrimidinyl, said phenyl, phenoxy, pyridyl and pyrimidinyl being optionally substituted by halo, -CN, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^7$, $-NR^5R^5$, -(C_1-C_6 alkylene)-NR^5R^5, C_1-C_6 alkyl, fluoro-(C_1-C_6)-alkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy;

R^9 is H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl, said C_1-C_6 alkyl and C_3-C_7 cycloalkyl being optionally substituted by $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-CONR^5R^5$ or R^6;

R^{10} is C_1-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_7 cycloalkyl, phenyl, benzyl or C-linked R^6, said C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-OCONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-OCONR^5CO_2R^7$, $-NR^5R^5$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5CO_2R^7$, $-NR^5CONR^5R^5$, $-NR^5COCONR^5R^5$, $-NR^5SO_2R^7$, $-SO_2NR^5R^5$ or R^6;

X is $-CH_2$-, $-CHR^{11}$-, -CO-, -S-, -SO- or $-SO_2$-;

R^{11} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, fluoro-(C_1-C_6)-alkyl or C_1-C_6 alkoxy; and

R^{12} is C_1-C_6 alkyl substituted by R^6, $-OR^5$, $-CONR^5R^5$, $-NR^5COR^5$ or $-NR^5R^5$;

in the manufacture of a reverse transcriptase inhibitor or modulator.

2. The use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in claim 1, in the manufacture of a medicament for the treatment of a human immunodeficiency viral (HIV), or genetically related retroviral, infection or a resulting acquired immunodeficiency syndrome (AIDS).

3. The use of claim 1 or claim 2, wherein R^1 is C_1-C_6 alkyl, $-OR^7$, $-CO_2R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5CO$-(C_1-C_6 alkylene)-OR^5 or R^6, said C_1-C_6 alkyl being optionally substituted by halo, -CN, $-OR^5$, $-OR^8$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^8R^9$, $-NR^5COR^5$, $-NR^5COR^6$, $-NR^5COR^8$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6.

4. The use of claim 3 wherein R^1 is C_1-C_6 alkyl, $-OR^7$, $-CO_2R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5CO$-(C_1-C_6 alkylene)-OR^5 or R^6, said C_1-C_6 alkyl being optionally substituted by halo or $-OR^5$.

5. The use of claim 4 wherein R^1 is C_1-C_3 alkyl, $-OCH_3$, $-CO_2(C_1$-C_2 alkyl), $-NHCO_2(C_1$-C_2 alkyl), $-NH_2$, $-N(CH_3)_2$, $-NHCOCH_2OCH_3$ or furanyl, said C_1-C_3 alkyl being optionally substituted by fluoro or -OH.

6. The use of claim 5 wherein R^1 is methyl, ethyl, prop-2-yl, hydroxymethyl, trifluoromethyl, $-OCH_3$, $-CO_2CH_2CH_3$, $-NHCO_2CH_2CH_3$, $-NH_2$, $-N(CH_3)_2$, $-NHCOCH_2OCH_3$ or furan-2-yl.

7. The use of claim 6 wherein R^1 is ethyl.

8. The use of claim 1 or claim 2 wherein R^1 is methyl, ethyl, trifluoromethyl or $-CH_2NHCH_2$(4-cyanophenyl).

9. The use of any one of the preceding claims wherein R^2 is H, C_1-C_6 alkyl, -(C_1-C_3 alkylene)-NR^5CO-(C_1-C_6 alkyl), -(C_1-C_3 alkylene)-NR^5CONR^5-(C_1-C_6 alkyl), -(C_1-C_3 alkylene)-NR^5CONR^5CO-(phenyl), -(C_1-C_3 alkylene)-NR^5SO_2(C-linked R^6), -(C_1-C_3 alkylene)-NR^5CO(C-linked R^6), -(C_1-C_3 alkylene)-NR^5CO-(phenyl), each C_1-C_6 alkyl and phenyl being optionally substituted by halo, $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-OCONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-OCONR^5CO_2R^7$, $-NR^5R^5$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5CO_2R^7$, $-NR^5CONR^5R^5$, $-NR^5COCONR^5R^5$, $-NR^5SO_2R^7$, $-SO_2NR^5R^5$ or R^6.

10. The use of claim 9 wherein R^2 is H, C_1-C_6 alkyl, -(C_1-C_3 alkylene)-NR^5CO-(C_1-C_6 alkyl), -(C_1-C_3 alkylene)-NR^5CONR^5-(C_1-C_6 alkyl), -(C_1-C_3 alkylene)-NR^5CONR^5CO-(phenyl), -(C_1-C_3 alkylene)-$NR^5SO_2R^6$, -(C_1-C_3 alkylene)-NR^5COR^6, -(C_1-C_3 alkylene)-NR^5CO-(phenyl), each C_1-C_6 alkyl and phenyl being optionally substituted by halo, $-OR^5$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-OCONR^5R^5$, $-OCONR^5CO_2R^7$, $-NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5COCONR^5R^5$ or R^6.

11. The use of claim 10 wherein R^2 is H, C_1-C_3 alkyl, -(C_1-C_2 alkylene)-NHCO-(C_1-C_3 alkyl), -(C_1-C_2 alkylene)-NHCONH-(C_1-C_3 alkyl), -(C_1-C_2 alkylene)-NHCONHCO-(phenyl), -(C_1-C_2 alkylene)-$NHSO_2R^6$, -(C_1-C_2 alkylene)-$NHCOR^6$, -(C_1-C_2 alkylene)-NHCO-(phenyl), each C_1-C_3 alkyl and phenyl being optionally substituted by fluoro, -OH, -O(C_1-C_6 alkyl), -CN, -CO_2(C_1-C_6 alkyl), -$CONH_2$, -$OCONH_2$, -$OCONHCO_2Ph$, -NH_2, -N(C_1-C_6 alkyl)$_2$, -$NHCONH_2$, -$NHCOCONH_2$ or R^6.

12. The use of any one of claims 9 to 11 wherein R^6 is 2,4-dihydroxypyrimidinyl, 1-methylimidazolyl, tetrahydrofuranyl, 1,5-dimethylpyrazolyl, tetrazolyl, pyridinyl, pyrimidinyl, 3-hydroxypyridazinyl, 2-hydroxypyridinyl, 2-oxo-2H-pyranyl or 1,2,3-thiadiazolyl.

13. The use of claim 11 wherein R^2 is H, -CH_2OH, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2OCONH_2, -$CH_2CH_2OCONH_2$, -$CH_2OCONHCO_2Ph$, -$CH_2CO_2CH_2CH_3$, -$CH_2CH_2CO_2CH_3$, -$CH_2CH_2CO_2CH_2CH_3$, -$CH_2CH_2CONH_2$, -$CH_2CH_2NH_2$, -$CH_2CH_2CH_2NH_2$, -$CH_2CH_2NHCOCHF_2$, -$CH_2CH_2NHCOCH_2CN$, -$CH_2CH_2NHCOCH_2N(CH_3)_2$, -$CH_2CH_2NHCOCH_2OCH_3$, -$CH_2CH_2NHCOCH_2OH$, -$CH_2CH_2NHCOCH_2OCH_2CH_3$, -$CH_2CH_2NHCOCH_2NHCONH_2$, -$CH_2CH_2NHCOCONH_2$, -$CH_2CH_2NHCONHCH_2CH_2CH_3$, -$CH_2CH_2NHCONHCOPh$, -$CH_2CH_2NHCONHCO$(2,6-difluorophenyl), -$CH_2CH_2NHSO_2$(2,4-dihydroxypyrimidin-5-yl), -$CH_2CH_2NHSO_2$(1-methylimidazol-4-yl), -CH_2CH_2NHCO(tetrahydrofuran-2-yl), -CH_2CH_2NHCO(1,5-dimethylpyrazol-3-yl), -$CH_2CH_2NHCOCH_2$(tetrazol-1-yl), -$CH_2CH_2NHCOPh$, -CH_2CH_2NHCO(pyridin-2-yl), -CH_2CH_2NHCO(pyrimidin-2-yl), -CH_2CH_2NHCO(2-fluorophenyl), -CH_2CH_2NHCO(3-hydroxyphenyl), -CH_2CH_2NHCO(3-hydroxypyridazin-6-yl), -CH_2CH_2NHCO(2-hydroxypyridin-6-yl), -CH_2CH_2NHCO(2-oxo-2H-pyran-5-yl) or -CH_2CH_2NHCO(1,2,3-thiadiazol-4-yl).

14. The use of any one of claims 1 to 8 wherein R^2 is H, methyl, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2NH_2$, -$CH_2CH_2CH_2NH_2$, -CH_2CN, -$CH_2CH_2OCH_3$, -CH_2CONH_2, -$CH_2CH_2NHCOCH_2OCH_3$ or azetidin-3-yl.

15. The use of claim 14 wherein R^2 is $-CH_2CH_2OH$, $-CH_2CH_2NH_2$, $-CH_2CN$ or azetidin-3-yl.

16. The use of any one of the preceding claims wherein R^3 is C_1-C_6 alkyl, $-CO_2R^5$, $-CONR^5R^5$, $-NR^5CO_2R^7$ or $-NR^5R^5$, said C_1-C_6 alkyl being optionally substituted by halo, -CN, $-OR^5$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5COR^5$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6.

17. The use of claim 16 wherein R^3 is C_1-C_6 alkyl, $-CO_2R^5$, $-CONR^5R^5$, $-NR^5CO_2R^5$ or $-NR^5R^5$, said C_1-C_6 alkyl being optionally substituted by halo, -CN or $-OR^5$.

18. The use of claim 17 wherein R^3 is C_1-C_3 alkyl, $-CO_2(C_1$-C_2 alkyl), $-CONH_2$, $-NHCO_2(C_1$-C_4 alkyl), $-N(CH_3)_2$ or $-NH_2$, said C_1-C_3 alkyl being optionally substituted by halo, -CN or -OH.

19. The use of claim 18 wherein R^3 is methyl, ethyl, prop-2-yl, hydroxymethyl, cyanomethyl, trifluoromethyl, $-CO_2CH_2CH_3$, $-CONH_2$, $-NHCO_2C(CH_3)_3$, $-N(CH_3)_2$ or $-NH_2$.

20. The use of claim 19 wherein R^3 is methyl, ethyl, prop-2-yl or trifluoromethyl.

21. The use of claim 20 wherein R^3 is ethyl.

22. The use of any one of the preceding claims wherein R^4 is phenyl optionally substituted by R^6, halo, -CN, C_1-C_6 alkyl, fluoro-(C_1-C_6)-alkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy.

23. The use of claim 22 wherein R^4 is phenyl substituted by halo, -CN or C_1-C_3 alkyl.

24. The use of claim 23 wherein R^4 is phenyl substituted by fluoro, chloro, bromo, -CN, or methyl.

25. The use of claim 24 wherein R^4 is 3-chlorophenyl, 4-chlorophenyl, 3-fluorophenyl, 3,5-dichlorophenyl, 2,6-difluorophenyl, 3,5-difluorophenyl, 3,5-dibromophenyl, 3,5-dicyanophenyl or 3,5-dimethylphenyl.

26. The use of claim 23 wherein R^4 is (i) phenyl substituted at the 3 position by fluoro, chloro, methyl or cyano or (ii) phenyl substituted at the 3 and 5 positions by two substituents independently chosen from fluoro, chloro, methyl and cyano.

27. The use of any one of the preceding claims wherein X is $-CH_2-$, $-CHR^{11}-$, -CO-, -S- or $-SO_2-$.

28. The use of claim 27 wherein X is $-CH_2-$, $-CH(OCH_3)-$, -CO-, -S- or $-SO_2-$.

29. The use of claim 28 wherein X is $-CH_2-$ or -S-.

30. The use of claim 1 or claim 2 wherein the compound of the formula (I) is selected from

2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3-chlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-difluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3-fluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dichlorobenzyl)-5-isopropyl-3-methyl-1*H*-pyrazol-1-yl]ethanol;
ethyl [4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]acetate;
ethyl [4-(3-fluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate;
N^1-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}ethanediamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-6-oxo-1,6-dihydro-3-pyridazinecarboxamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-1,5-dimethyl-1*H*-pyrazole-3-carboxamide;

2-[(aminocarbonyl)amino]-*N*-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}acetamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2-ethoxyacetamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2-pyridinecarboxamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2-methoxyacetamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-6-oxo-1,6-dihydro-2-pyridinecarboxamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2-pyrazinecarboxamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2-oxo-2*H*-pyran-5-carboxamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2-(1*H*-tetraazol-1-yl)acetamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}tetrahydro-2-furancarboxamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-3-hydroxybenzamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2-hydroxyacetamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-1,2,3-thiadiazole-4-carboxamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2-(dimethylamino)acetamide;

2-cyano-*N*-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}acetamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2-fluorobenzamide;

N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-*N'*-propylurea;

N-benzoyl-*N'*-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}urea;

2-[4-(3,5-dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]ethanol;

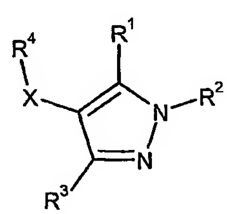
ethyl [4-(3,5-dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate;
ethyl [4-(3,5-dichlorobenzyl)-5-isopropyl-3-methyl-1*H*-pyrazol-1-yl]acetate;
4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazole;
2-[4-(3,5-dichlorobenzyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dichlorobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol;
2-{4-[(4-chlorophenyl)sulfanyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol;
ethyl [4-(3-chlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate;
ethyl [4-(3,5-difluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-1-yl]acetate;
4-(3,5-dichlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole;
4-(3,5-difluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole;
4-(3-fluorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole;
4-(3-chlorobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazole;
2-{4-[(3,5-dichlorophenyl)sulfanyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol;
2-{4-[(3,5-dichlorophenyl)sulfonyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol;
4-(3,5-dichlorobenzyl)-3,5-dimethyl-1*H*-pyrazole;
2-[4-(3,5-dichlorobenzyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethanamine;
2-[4-(3,5-dichlorobenzyl)-5-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dichlorobenzyl)-3-ethyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dichlorobenzyl)-5-ethyl-3-methyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dichlorobenzyl)-3-ethyl-5-methyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dichlorobenzyl)-3-(dimethylamino)-5-methyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dimethylbenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dichlorobenzyl)-5-methoxy-3-methyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dichlorobenzyl)-5-(2-furyl)-3-methyl-1*H*-pyrazol-1-yl]ethanol;
(3,5-dichlorophenyl)[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]methanone;
(±)-2-{4-[(3,5-dichlorophenyl)(methoxy)methyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol;
2-[4-(2,6-difluorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanol;
2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl carbamate;
methyl 3-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]propanoate;
ethyl 3-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]propanoate;
3-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]propanamide;

3-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]-1-propanol;
[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]methanol;
[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl carbamate;
2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethanamine;
N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}benzamide;
N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-1-methyl-1*H*-imidazole-4-sulfonamide;
ethyl 4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazole-3-carboxylate;
ethyl 4-[(3,5-dichlorophenyl)sulfanyl]-3-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazole-5-carboxylate;
4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazole-3-carboxamide;
2-[4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-3-(hydroxymethyl)-1*H*-pyrazol-1-yl]ethanol;
3-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]-1-propanamine;
2-[4-[(3,5-dichlorophenyl)sulfanyl]-3-ethyl-5-(hydroxymethyl)-1*H*-pyrazol-1-yl]ethanol;
N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2,2-difluoroacetamide;
[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]methyl phenyl imidodicarbonate;
N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-*N*'-(2,6-difluorobenzoyl)urea;
N-{2-[4-(3,5-dichlorobenzyl)-3,5-diethyl-1*H*-pyrazol-1-yl]ethyl}-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinesulfonamide;
ethyl 4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1*H*-pyrazole-3-carboxylate;
[4-[(3,5-dichlorophenyl)sulfanyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-3-yl]acetonitrile;
[4-[(3,5-dichlorophenyl)sulfonyl]-5-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-3-yl]acetonitrile;
2-{4-[(3,5-dichlorophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol;
4-(3,5-dichlorobenzyl)-3-ethyl-1*H*-pyrazol-5-amine;
ethyl 4-(3,5-dichlorobenzyl)-3-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-5-ylcarbamate;

N-[4-(3,5-dichlorobenzyl)-3-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-5-yl]-2-methoxyacetamide;
2-[4-(3,5-dichlorobenzyl)-5-(dimethylamino)-3-ethyl-1*H*-pyrazol-1-yl]ethanol;
ethyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carboxylate;
ethyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazole-5-carboxylate;
tert-butyl 4-(3,5-dichlorobenzyl)-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazol-3-ylcarbamate;
2-[3-amino-4-(3,5-dichlorobenzyl)-5-methyl-1*H*-pyrazol-1-yl]ethanol;
ethyl [4-(3,5-dichlorobenzyl)-5-methoxy-3-methyl-1*H*-pyrazol-1-yl]acetate;
2-[5-amino-4-(3,5-dichlorobenzyl)-3-ethyl-1*H*-pyrazol-1-yl]ethanol;
5-{[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]methyl}isophthalonitrile;
5-[(3,5-diethyl-1*H*-pyrazol-4-yl)methyl]isophthalonitrile;
5-{[1-(2-aminoethyl)-3,5-diethyl-1*H*-pyrazol-4-yl]methyl}isophthalonitrile;
2-{4-[(3,5-dibromophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol; and
5-{[3,5-diethyl-1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]sulfanyl}isophthalonitrile;

and the pharmaceutically acceptable salts and solvates thereof.

31. The use of a compound of the formula



(Ia)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, $-OR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-NR^5CO_2R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$, $-NR^5CONR^6R^7$, $-NR^5SO_2R^6$ or R^8, said C_1-C_6 alkyl, phenyl and benzyl being optionally substituted by halo, $-OR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-NR^5CO_2R^6$,

$-NR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$, $-NR^5CONR^6R^7$, $-NR^5SO_2R^6$ or R^8;

R^2 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl or C-linked R^{12}, said C_1-C_6 alkyl, phenyl and benzyl being optionally substituted by $-OR^9$, $-CO_2R^9$, $-CO_2NR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{10}$ or R^{12};

R^3 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, $-OR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-OCONR^{13}R^{14}$, $-NR^{13}CO_2R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-SO_2NR^{13}R^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}SO_2R^{14}$ or R^{16}, said C_1-C_6 alkyl, phenyl and benzyl being optionally substituted by halo, $-OR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-OCONR^{13}R^{14}$, $-NR^{13}CO_2R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-SO_2NR^{13}R^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}SO_2R^{14}$ or R^{16};

R^4 is phenyl or pyridyl, each being optionally substituted by halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy;

R^5, R^6, R^7, R^9, R^{10}, R^{11}, R^{13}, R^{14} and R^{15} are either each H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl or, when two such groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached may represent azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl and morpholinyl being optionally substituted by C_1-C_6 alkyl or C_3-C_7 cycloalkyl;

R^8, R^{12} and R^{16} are each a five- or six-membered heterocyclic group containing 1 to 4 heteroatoms selected from O, N and S and optionally substituted by oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl or halo; and

X is $-CH_2-$, -S-, -SO- or $-SO_2-$;

in the manufacture of a reverse transcriptase inhibitor.

32. The use of a compound of the formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, as defined in claim 31, in the manufacture of a medicament for the treatment of a human immunodeficiency viral (HIV), or genetically related retroviral, infection or a resulting acquired immunodeficiency syndrome (AIDS).

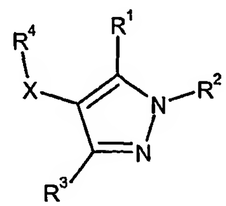
33. A compound of the formula (I), as defined in any one of claims 1 or 3 to 30, or a compound of the formula (Ia), as defined in claim 31, or a pharmaceutically acceptable salt or solvate of either, for use as a reverse transcriptase inhibitor.

34. A compound of the formula (I), as defined in any one of claims 1 or 3 to 30, or a compound of the formula (Ia), as defined in claim 31, or a pharmaceutically acceptable salt or solvate of either, for use in the treatment of a human immunodeficiency viral (HIV), or genetically related retroviral, infection or a resulting acquired immunodeficiency syndrome (AIDS).

35. A method of treatment of a disorder treatable by the inhibition of reverse transcriptase, comprising the administration of an effective amount of a compound of the formula (I), as defined in any one of claims 1 or 3 to 30, or a compound of the formula (Ia), as defined in claim 31, or a pharmaceutically acceptable salt or solvate of either, to a patient in need of such treatment.

36. A method of treatment of a human immunodeficiency viral (HIV), or genetically related retroviral, infection or a resulting acquired immunodeficiency syndrome (AIDS) comprising the administration of an effective amount of a compound of the formula (I), as defined in any one of claims 1 or 3 to 30, or a compound of the formula (Ia), as defined in claim 31, or a pharmaceutically acceptable salt or solvate of either, to a patient in need of such treatment.

37. A compound of the formula



(Ib)

or a pharmaceutically acceptable salt or solvate thereof, wherein

either (i) R^1 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, halo, -CN, $-OR^7$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5CO$-(C_1-C_6 alkylene)-OR^5, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6, said C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, $-OR^5$, $-OR^8$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^8R^9$, $-NR^5COR^5$, $-NR^5COR^6$, $-NR^5COR^8$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6 and

R^2 is -Y-Z,

or, R^1 and R^2, when taken together, represent unbranched C_3-C_4 alkylene, optionally wherein one methylene group of said C_3-C_4 alkylene is replaced by an oxygen atom or a nitrogen atom, said nitrogen atom being optionally substituted by R^5 or R^8,

and R^3 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, -CN, halo, $-OR^7$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5COR^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6, said C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, $-OR^5$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5COR^5$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6,

or (ii) R^1 and R^3 are each independently C_1-C_6 alkyl, C_3-C_7 cycloalkyl or halo-(C_1-C_6 alkyl), and R^2 is H,

provided that

(a) for definition (i), R^1 and R^3 are not both H,

(b) for definition (i), R^1 and R^3 are not both optionally substituted phenyl, as defined therein,

(c) for definition (i), when R^1 and R^3 are both methyl, R^2 is not phenyl or methyl, and

(d) for definition (ii), R^1 and R^3 are not both methyl;

Y is a direct bond or C_1-C_3 alkylene;

Z is R^{10} or, where Y is C_1-C_3 alkylene, Z is $-NR^5COR^{10}$, $-NR^5CONR^5R^{10}$, $-NR^5CONR^5COR^{10}$ or $-NR^5SO_2R^{10}$;

R^4 is phenyl or pyridyl, each substituted by at least one substituent selected from halo, -CN, C_1-C_6 alkyl, fluoro-(C_1-C_6)-alkyl, C_3-C_7 cycloalkyl and C_1-C_6 alkoxy;

each R^5 is independently either H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, fluoro-(C_1-C_6)-alkyl, phenyl or benzyl, or, when two such groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl and morpholinyl being optionally substituted by C_1-C_6 alkyl or C_3-C_7 cycloalkyl and said piperazinyl and homopiperazinyl being optionally substituted on the nitrogen atom not taken together with the two R^5 groups to form the ring by $-COR^7$ or $-SO_2R^7$;

R^6 is a four to six-membered, aromatic, partially unsaturated or saturated heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s), said heterocyclic group being optionally substituted by

$-OR^5$, $-NR^5R^5$, -CN, oxo, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, $-COR^7$ or halo;

R^7 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, fluoro-(C_1-C_6)-alkyl, phenyl or benzyl;

R^8 is C_1-C_6 alkyl substituted by phenyl, pyridyl or pyrimidinyl, said phenyl, pyridyl and pyrimidinyl being optionally substituted by halo, -CN, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^7$, $-NR^5R^5$, -(C_1-C_6 alkylene)-NR^5R^5, C_1-C_6 alkyl, fluoro-(C_1-C_6)-alkyl, C_3-C_7 cycloalkyl or C_1-C_6 alkoxy;

R^9 is H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl, said C_1-C_6 alkyl and C_3-C_7 cycloalkyl being optionally substituted by $-OR^5$, $-NR^5R^5$, $-NR^5COR^5$, $-CONR^5R^5$ or R^6;

R^{10} is (a) benzyl or C-linked R^6, said benzyl being optionally substituted by halo, $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-OCONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-OCONR^5CO_2R^7$, $-NR^5R^5$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5CO_2R^7$, $-NR^5CONR^5R^5$, $-NR^5COCONR^5R^5$, $-NR^5SO_2R^7$, $-SO_2NR^5R^5$ or R^6, or (b) when R^1 and R^3 are each independently C_1-C_6 alkyl, C_3-C_7 cycloalkyl or halo-(C_1-C_6 alkyl), R^{10} is phenyl, C_1-C_6 alkyl or C_3-C_7 cycloalkyl each being optionally substituted by halo, $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-OCONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-OCONR^5CO_2R^7$, $-NR^5R^5$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5CO_2R^7$, $-NR^5CONR^5R^5$, $-NR^5COCONR^5R^5$, $-NR^5SO_2R^7$, $-SO_2NR^5R^5$ or R^6;

X is $-CH_2-$, $-CHR^{11}-$, -CO-, -S-, -SO- or $-SO_2-$;

R^{11} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, fluoro-(C_1-C_6)-alkyl or C_1-C_6 alkoxy; and

R^{12} is C_1-C_6 alkyl substituted by R^6, $-OR^5$, $-CONR^5R^5$, $-NR^5COR^5$ or $-NR^5R^5$.

38. A compound as claimed in claim 37 wherein R^1 is C_1-C_6 alkyl, $-OR^7$, $-CO_2R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5CO$-(C_1-C_6 alkylene)-OR^5 or R^6, said C_1-C_6 alkyl being optionally substituted by halo, -CN, $-OR^5$, $-OR^8$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$,

$-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^8R^9$, $-NR^5COR^5$, $-NR^5COR^6$, $-NR^5COR^8$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6.

39. A compound as claimed in claim 38 wherein R^1 is C_1-C_6 alkyl, $-OR^7$, $-CO_2R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5CO$-(C_1-C_6 alkylene)-OR^5 or R^6, said C_1-C_6 alkyl being optionally substituted by halo or $-OR^5$.

40. A compound as claimed in claim 39 wherein R^1 is C_1-C_3 alkyl, $-OCH_3$, $-CO_2$(C_1-C_2 alkyl), $-NHCO_2$(C_1-C_2 alkyl), $-NH_2$, $-N(CH_3)_2$, $-NHCOCH_2OCH_3$ or furanyl, said C_1-C_3 alkyl being optionally substituted by fluoro or -OH.

41. A compound as claimed in claim 40 wherein R^1 is methyl, ethyl, prop-2-yl, hydroxymethyl, trifluoromethyl, $-OCH_3$, $-CO_2CH_2CH_3$, $-NHCO_2CH_2CH_3$, $-NH_2$, $-N(CH_3)_2$, $-NHCOCH_2OCH_3$ or furan-2-yl.

42. A compound as claimed in claim 41 wherein R^1 is ethyl.

43. A compound as claimed in claim 37 wherein R^1 is methyl, ethyl, trifluoromethyl or $-CH_2NHCH_2$(4-cyanophenyl).

44. A compound as claimed in any one of claims 37 to 43 wherein R^2 is H, C_1-C_6 alkyl, -(C_1-C_3 alkylene)-NR^5CO-(C_1-C_6 alkyl), -(C_1-C_3 alkylene)-NR^5CONR^5-(C_1-C_6 alkyl), -(C_1-C_3 alkylene)-NR^5CONR^5CO-(phenyl), -(C_1-C_3 alkylene)-NR^5SO_2(C-linked R^6), -(C_1-C_3 alkylene)-NR^5CO(C-linked R^6), -(C_1-C_3 alkylene)-NR^5CO-(phenyl), each C_1-C_6 alkyl and phenyl being optionally substituted by halo, $-OR^5$, $-OR^{12}$, -CN, $-CO_2R^7$, $-CONR^5R^5$, $-OCONR^5R^5$, $-C(=NR^5)NR^5OR^5$, $-CONR^5NR^5R^5$, $-OCONR^5CO_2R^7$, $-NR^5R^5$, $-NR^5R^{12}$, $-NR^5COR^5$, $-NR^5CO_2R^7$, $-NR^5CONR^5R^5$, $-NR^5COCONR^5R^5$, $-NR^5SO_2R^7$, $-SO_2NR^5R^5$ or R^6.

45. A compound as claimed in claim 44 wherein R^2 is H, C_1-C_6 alkyl, -(C_1-C_3 alkylene)-NR^5CO-(C_1-C_6 alkyl), -(C_1-C_3 alkylene)-NR^5CONR^5-(C_1-C_6 alkyl), -(C_1-C_3

alkylene)-NR^5CONR^5CO-(phenyl), -(C_1-C_3 alkylene)-$NR^5SO_2R^6$, -(C_1-C_3 alkylene)-NR^5COR^6, -(C_1-C_3 alkylene)-NR^5CO-(phenyl), each C_1-C_6 alkyl and phenyl being optionally substituted by halo, -OR^5, -CN, -CO_2R^7, -$CONR^5R^5$, -$OCONR^5R^5$, -$OCONR^5CO_2R^7$, -NR^5R^5, -$NR^5CONR^5R^5$, -$NR^5COCONR^5R^5$ or R^6.

46. A compound as claimed in claim 45 wherein R^2 is H, C_1-C_3 alkyl, -(C_1-C_2 alkylene)-NHCO-(C_1-C_3 alkyl), -(C_1-C_2 alkylene)-NHCONH-(C_1-C_3 alkyl), -(C_1-C_2 alkylene)-NHCONHCO-(phenyl), -(C_1-C_2 alkylene)-$NHSO_2R^6$, -(C_1-C_2 alkylene)-$NHCOR^6$, -(C_1-C_2 alkylene)-NHCO-(phenyl), each C_1-C_3 alkyl and phenyl being optionally substituted by fluoro, -OH, -O(C_1-C_6 alkyl), -CN, -CO_2(C_1-C_6 alkyl), -$CONH_2$, -$OCONH_2$, -$OCONHCO_2Ph$, -NH_2, -N(C_1-C_6 alkyl)$_2$, -$NHCONH_2$, -$NHCOCONH_2$ or R^6.

47. A compound as claimed in any one of claims 44 to 46 wherein R^6 is 2,4-dihydroxypyrimidinyl, 1-methylimidazolyl, tetrahydrofuranyl, 1,5-dimethylpyrazolyl, tetrazolyl, pyridinyl, pyrimidinyl, 3-hydroxypyridazinyl, 2-hydroxypyridinyl, 2-oxo-2H-pyranyl or 1,2,3-thiadiazolyl.

48. A compound as claimed in claim 46 wherein R^2 is H, -CH_2OH, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2OCONH_2, -$CH_2CH_2OCONH_2$, -$CH_2OCONHCO_2Ph$, -$CH_2CO_2CH_2CH_3$, -$CH_2CH_2CO_2CH_3$, -$CH_2CH_2CO_2CH_2CH_3$, -$CH_2CH_2CONH_2$, -$CH_2CH_2NH_2$, -$CH_2CH_2CH_2NH_2$, -$CH_2CH_2NHCOCHF_2$, -$CH_2CH_2NHCOCH_2CN$, -$CH_2CH_2NHCOCH_2N(CH_3)_2$, -$CH_2CH_2NHCOCH_2OCH_3$, -$CH_2CH_2NHCOCH_2OH$, -$CH_2CH_2NHCOCH_2OCH_2CH_3$, -$CH_2CH_2NHCOCH_2NHCONH_2$, -$CH_2CH_2NHCOCONH_2$, -$CH_2CH_2NHCONHCH_2CH_2CH_3$, -$CH_2CH_2NHCONHCOPh$, -$CH_2CH_2NHCONHCO$(2,6-difluorophenyl), -$CH_2CH_2NHSO_2$(2,4-dihydroxypyrimidin-5-yl), -$CH_2CH_2NHSO_2$(1-methylimidazol-4-yl), -CH_2CH_2NHCO(tetrahydrofuran-2-yl), -CH_2CH_2NHCO(1,5-dimethylpyrazol-3-yl), -$CH_2CH_2NHCOCH_2$(tetrazol-1-yl), -$CH_2CH_2NHCOPh$, -CH_2CH_2NHCO(pyridin-2-yl), -CH_2CH_2NHCO(pyrimidin-2-yl), -CH_2CH_2NHCO(2-fluorophenyl), -CH_2CH_2NHCO(3-hydroxyphenyl), -CH_2CH_2NHCO(3-hydroxypyridazin-6-yl), -CH_2CH_2NHCO(2-hydroxypyridin-6-yl),

$-CH_2CH_2NHCO$(2-oxo-2H-pyran-5-yl) or $-CH_2CH_2NHCO$(1,2,3-thiadiazol-4-yl).

49. A compound as claimed in claim 37 wherein R^2 is H, methyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2NH_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2CN$, $-CH_2CH_2OCH_3$, $-CH_2CONH_2$, $-CH_2CH_2NHCOCH_2OCH_3$ or azetidin-3-yl.

50. A compound as claimed in claim 49 wherein R^2 is $-CH_2CH_2OH$, $-CH_2CH_2NH_2$, $-CH_2CN$ or azetidin-3-yl.

51. A compound as claimed in any one of claims 37 to 50 wherein R^3 is C_1-C_6 alkyl, $-CO_2R^5$, $-CONR^5R^5$, $-NR^5CO_2R^7$ or $-NR^5R^5$, said C_1-C_6 alkyl being optionally substituted by halo, -CN, $-OR^5$, $-CO_2R^5$, $-CONR^5R^5$, $-OCONR^5R^5$, $-NR^5CO_2R^7$, $-NR^5R^5$, $-NR^5COR^5$, $-SO_2NR^5R^5$, $-NR^5CONR^5R^5$, $-NR^5SO_2R^7$ or R^6.

52. A compound as claimed in claim 51 wherein R^3 is C_1-C_6 alkyl, $-CO_2R^5$, $-CONR^5R^5$, $-NR^5CO_2R^7$ or $-NR^5R^5$, said C_1-C_6 alkyl being optionally substituted by halo, -CN or $-OR^5$.

53. A compound as claimed in claim 52 wherein R^3 is C_1-C_3 alkyl, $-CO_2(C_1$-C_2 alkyl), $-CONH_2$, $-NHCO_2(C_1$-C_4 alkyl), $-N(CH_3)_2$ or $-NH_2$, said C_1-C_3 alkyl being optionally substituted by halo, -CN or -OH.

54. A compound as claimed in claim 53 wherein R^3 is methyl, ethyl, prop-2-yl, hydroxymethyl, cyanomethyl, trifluoromethyl, $-CO_2CH_2CH_3$, $-CONH_2$, $-NHCO_2C(CH_3)_3$, $-N(CH_3)_2$ or $-NH_2$.

55. A compound as claimed in claim 54 wherein R^3 is methyl, ethyl, prop-2-yl or trifluoromethyl.

56. A compound as claimed in claim 55 wherein R^3 is ethyl.

57. A compound as claimed in any one of claims 37 to 56 wherein R^4 is phenyl substituted by at least one substituent selected from halo, -CN, C_1-C_6 alkyl, fluoro-(C_1-C_6)-alkyl, C_3-C_7 cycloalkyl and C_1-C_6 alkoxy.

58. A compound as claimed in claim 57 wherein R^4 is phenyl substituted by at lease one substituent selected from halo, -CN and C_1-C_3 alkyl.

59. A compound as claimed in claim 58 wherein R^4 is phenyl substituted by at least one substituent selected from fluoro, chloro, bromo, -CN and methyl.

60. A compound as claimed in claim 59 wherein R^4 is 3-chlorophenyl, 4-chlorophenyl, 3-fluorophenyl, 3,5-dichlorophenyl, 2,6-difluorophenyl, 3,5-difluorophenyl, 3,5-dibromophenyl, 3,5-dicyanophenyl or 3,5-dimethylphenyl.

61. A compound as claimed in claim 58 wherein R^4 is (i) phenyl substituted at the 3 position by fluoro, chloro, methyl or cyano or (ii) phenyl substituted at the 3 and 5 positions by two substituents independently chosen from fluoro, chloro, methyl and cyano.

62. A compound as claimed in any one of claims 37 to 61 wherein X is $-CH_2-$, $-CHR^{11}-$, -CO-, -S- or $-SO_2-$.

63. A compound as claimed in claim 62 wherein X is $-CH_2-$, $-CH(OCH_3)-$, -CO-, -S- or $-SO_2-$.

64. A compound as claimed in claim 63 wherein X is $-CH_2-$ or -S-.

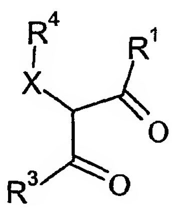
65. A compound as defined in claim 30.

66. A pharmaceutical composition including a compound of the formula (Ib) or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 37 to 65, together with a pharmaceutically acceptable excipient, diluent or carrier.

67. A compound of the formula (Ib) or a pharmaceutically acceptable salt, solvate or composition thereof, as defined in any one of claims 37 to 65 and 66, respectively, for use as a medicament.

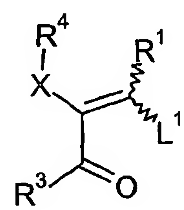
68. A process for the preparation of a compound of the formula (Ib), as defined in claim 37, wherein R^1 and R^3 are each either H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, benzyl, -NH_2, -CO_2R^5, -$CONR^5R^5$, or C-linked R^6, optionally substituted where allowed, which includes the reaction of

(a) a compound of the formula



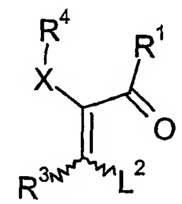
(II)

wherein R^1, R^3 and R^4 are as defined in claim 37, or a functional equivalent thereof, particularly a compound of the formula



(IV)

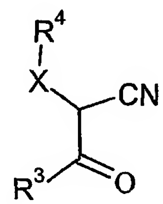
wherein R^1, R^3, R^4 and X are as defined in claim 37 and L^1 is a suitable leaving group, preferably dimethylamino, or a compound of the formula



(V)

wherein R^1, R^3, R^4 and X are as defined in claim 37 and L^2 is a suitable leaving group, preferably dimethylamino; or

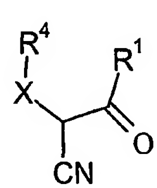
(b) a compound of the formula



(XXX)

wherein R^3, R^4 and X are as defined in claim 37; or

(c) a compound of the formula



(XXXII)

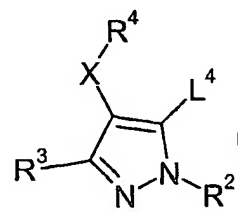
wherein R^1, R^4 and X are as defined in claim 37;

with a compound of the formula

$$H_2NNHR^2 \text{ (III)},$$

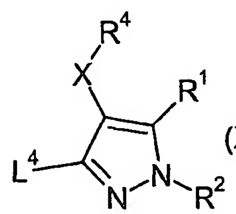
wherein R^2 is as defined in claim 37, or a salt or solvate thereof, optionally followed by the conversion of the compound of the formula (Ib) to a pharmaceutically acceptable salt thereof.

69. A process for the preparation of a compound of the formula (Ib), as defined in claim 37, wherein R^1 or R^3 is $-OR^7$, or a pharmaceutically acceptable salt or solvate thereof, which includes the reaction of a compound of the formula



(XVII)

wherein R^1, R^3, R^4 and X are as defined in claim 37 and L^4 is a suitable leaving group, preferably trifluoromethanesulphonate; or a compound of the formula



(XXI)

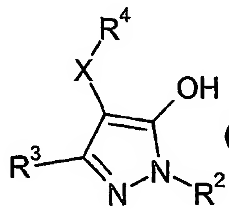
wherein R^1, R^3, R^4 and X are as defined in claim 37 and L^4 is a suitable leaving group, preferably trifluoromethanesulphonate;

with a compound of the formula

R^7OH (XXV)

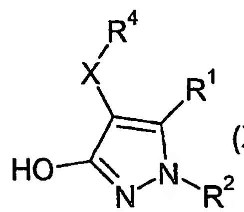
wherein R^7 is as defined in claim 37, in the presence of a suitable catalyst, preferably a suitable palladium catalyst, optionally followed by the conversion of the compound of the formula (Ib) to a pharmaceutically acceptable salt thereof.

70. A process for the preparation of a compound of the formula (Ib), as defined in claim 37, wherein R^1 or R^3 is $-OR^7$, or a pharmaceutically acceptable salt or solvate thereof, which includes the reaction of a compound of the formula



(XVIII)

wherein R^2, R^3, R^4 and X are as defined in claim 37, or a compound of the formula



(XXII)

wherein R^1, R^2, R^4 and X are as defined in claim 37, with a compound of the formula

R^7OH (XXV)

wherein R^7 is as defined in claim 37, under dehydrating conditions, preferably in the presence of a dialkylazodicarboxylate such as diethylazodicarboxylate, and a triarylphosphine such as triphenylphosphine, optionally followed by the conversion of the compound of the formula (Ib) to a pharmaceutically acceptable salt thereof.

71. A process for the preparation of a compound of the formula (Ib), as defined in claim 37, wherein R^1 or R^3 is $-OR^7$, or a pharmaceutically acceptable salt or solvate thereof, which includes the reaction of a compound of the formula (XVIII), as defined in claim 70, or a compound of the formula (XXII), as defined in claim 70, with a compound of the formula

$$R^7L^7 \text{ (XXIX)}$$

wherein R^7 is as defined in claim 37 and L^7 is a suitable leaving group, preferably halo, optionally followed by the conversion of the compound of the formula (Ib) to a pharmaceutically acceptable salt thereof.

72. A process for the preparation of a compound of the formula (Ib), as defined in claim 37, wherein R^1 or R^3 is $-OCONR^5R^5$, or a pharmaceutically acceptable salt or solvate thereof, which includes the reaction of a compound of the formula (XVIII), as defined in claim 70, or a compound of the formula (XXII), as defined in claim 70, with a compound of the formula

$$R^5R^5NCOL^5 \text{ (XXVI)}$$

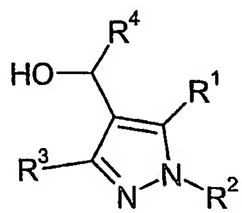
in which R^5 is as defined in claim 37 and L^5 is a suitable leaving group, preferably chloro, or with a compound of the formula

$$R^5N{=}C{=}O \text{ (XXVII)}$$

in which R^5 is as defined in claim 37, optionally followed by the conversion of the compound of the formula (Ib) to a pharmaceutically acceptable salt thereof.

73. A process for the preparation of a compound of the formula (Ib), as defined in claim 37, wherein X is -CO- or -CHR^{10}- and R^{10} is C_1-C_6 alkoxy, or a pharmaceutically acceptable salt or solvate thereof, which includes

(a) the oxidation of a compound of the formula



(XXXIV)

wherein R^1, R^2, R^3 and R^4 are as defined in claim 37, or

(b) the reaction of a compound of the formula (XXXIV), as defined above, with a compound of the formula

R^bL^8 (XXXVIII)

wherein R^b is C_1-C_6 alkyl and L^8 is a suitable leaving group, preferably chloro, bromo or iodo, optionally followed by the conversion of the compound of the formula (Ib) to a pharmaceutically acceptable salt thereof.

74. A process for the preparation of a compound of the formula (Ib), as defined in claim 37, containing an -OH, -NH- or -NH_2 group or a pharmaceutically acceptable salt or solvate thereof, which includes the deprotection of a corresponding compound bearing an -OP^1, -NP^1- or -NHP^1 group, respectively, wherein the group P^1 is a suitable protecting group, optionally followed by the conversion of the compound of the formula (Ib) to a pharmaceutically acceptable salt thereof.

75. A compound as defined in claim 65, selected from

2-{4-[(3,5-dichlorophenyl)sulfanyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanol;
2-[4-[(3,5-dichlorophenyl)sulfanyl]-3-ethyl-5-(hydroxymethyl)-1*H*-pyrazol-1-yl]ethanol; and
2-{4-[(3,5-dichlorophenyl)sulfanyl]-3,5-diethyl-1*H*-pyrazol-1-yl}ethanol.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/01174

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/12 C07D231/18 C07D405/04 C07D403/12 C07D231/14 C07D231/38 C07D231/40 A61K31/415 C07D401/12 C07D405/12 C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	M J GENIN: "NOVEL 1,5-DIPHENYLPYRAZOLE NONNUCLEOSIDE HIV-1 REVERSE TRANSCRIPTASE INHIBITORS" JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, 2000, pages 1034-1040, XP002178918 cited in the application See Tables 2 and 3 ---	1-75
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X	EP 0 959 074 A (PFIZER) 24 November 1999 (1999-11-24) see formula I, defintion (i) for Z ---	37-57, 66-74
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 October 2001	16/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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A	EP 0 846 686 A (PFIZER LTD ;PFIZER (US)) 10 June 1998 (1998-06-10) the whole document	1-75
A	EP 0 786 455 A (SHIONOGI & CO) 30 July 1997 (1997-07-30) cited in the application the whole document	1-75
A	US 3 303 200 A (FLANIGAN DONALD J ET AL) 7 February 1967 (1967-02-07) the whole document	1-75
X	PATENT ABSTRACTS OF JAPAN vol. 009, no. 059 (C-270), 15 March 1985 (1985-03-15) & JP 59 196869 A (SANKYO KK), 8 November 1984 (1984-11-08) compounds of RN 95115-05-2,95115-06-3 and 95115-07-4, 1,3 dimethyl, 4-CO(2,4diCl)Ph, 5 ((CH2)2Br or (CH2)3Br or (CH2)4Br) abstract	37

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,31(partly)

Present claims 1,31 relate to a use defined by reference to a desirable characteristic or property, namely the manufacture of a reverse transcriptase inhibitor or modulator.
The claims cover all uses having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such uses. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the use by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the use of the compound of formula I in the manufacture of a medicament for the treatment of HIV or AIDS.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 01/01174

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[redacted]ional Application No

PCT/IB 01/01174

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